# CENTER FOR DRUG EVALUATION AND RESEARCH APPROVAL PACKAGE FOR: APPLICATION NUMBER

**NDA 21-704** 

**Administrative/Correspondence Reviews** 



### Paragraph II Certification

Pursuant to 21 U.S.C. Sec. 355(b)(2)(A)(ii) and 21 CFR Sec. 314.50(i)(1)(i)(A)(2), Aventis Pharmaceuticals, Inc. certifies that in the opinion of the company and to the best of its knowledge, patent number 4576604 has expired.

Authorized signature of attorney, Agent, Representative or Authorized Officia

Date - February 16, 2004

Charlotte L. Barney Director, Global Patent Litigation

Aventis Pharmaceuticals, Inc. 1041 Route 202-206 P.O. Box 6800 Bridgewater, NJ 08807-0800

Telephone Number 908-231-4551

### 13. PATENT INFORMATION

Appears This Way On Original DEC. 11. 2003 12:02PM

PATENT LITIGATION-

\_\_NO. 5820\_\_\_\_P. 3\_

	Department of Health and Human Services Food and Drug Administration				
PATENT INFORMATION SUBMI		Suc CAM Bullemont att Phips S. NDA HUNGER			
FILING OF AN NDA, AMENDMENT,	,	21-704			
For Each Patent That Claims a D (Active Ingredient), Drug Product (	NAME OF APPLICANT / NOA NOLDER Avereis Plearmscoaticals Inc.				
Composition) and/or Metho					
The following in provided in accordance with	Bection \$15(b) and (c) of the	Padent Food, Drug, and Cosmello Act.			
TRADE NAME (ON PROPOSED TRADE NAME) Allegra-D 24 Hour					
ACTIVE INCHEDIENTIA	SYRENGTHIS)				
First females by throbloride Pseudosephetrine Dydroch	Exclanative by the million rule / Perudosephetisine Dydmichles ido 180mg/2-10mg				
DOBAGE PORM Tablet					
This pateral declaration form is required to se ston amendment, or supplement as required by 21 CPR 314.33 Within thiny (30) days after approved of an NDA or au declaration mean be submitted pursuant to 21 CPR 37 especies. The information succeived in the declaration by PDA for tating a pateral in the Crange Scots.	al the address provided in 21 Cl polomoni, or within Evry (30) 16 Edga(2)(0) with all of the c	FR \$14.53(d)(4). days of igauence of a new peacht, a new palent regured information based on the approved NDA			
For hand-written or typewriter versions (only) of I that does not require a "Yes" or "No" response), please					
PDA will not list patent information if you the a patent is not eligible for fating.	n incomplete patent declar	ution or the patent declaration indicates the			
For each patent submitted for the pending NEA.	smendment, or supplemen	referenced above, you must submit all the			
Information described below. If you are not sub- complete above section and sections 5 and 6.	MINING ANY PRIPAGE FOR THE	s panding MDA, smandment, or supplement,			
1. GENERAL		,			
n. Urmed States Perved Hurroom 5,578,610	0. lastro Desar of Peters 11/26/1996	c. Expiration Date of Palant 11/26/2013			
d. Name of Patent Owner	Address (of Paleis Owner)				
AMK (Cochadogy	5429 Main Street				
	P.O. Box 2587				
	Manchester Canson, Vermon	1			
	27P Code 05235-2587	FAX Inimber (7 smillstril) 802-362-3264			
	Telephone Number	E-Mail Address (F aveighte)			
	\$02-362-515R	davidw@afbrantecular.com			
a. Nillato of agent or competinging who resides or marriages a phose of susmoos within the United Square authorized to recond notion of pations conflication under section 80%(b)(3) and q)(2)(8) of the Federal Foot), Drug, and	Address (of agent or represents	tive rupined in 1, n.;			
Committee Act and 21 CPR 314.32 and 314.66 (C payed owner or NDA grationarholder does not restee or have a passe of business within the United States)	Chyristers				
<b>♂</b>	ZIP Code	FAX Number (Karminble)			
	1 stopnone Number	E Mad Address (V moderbie)			
L. Is the palant referenced above a patrol that had been subin					
approved MDA or supplement referenced above?  8. If the peters (elevenced shows has been extended previous	•	☐ Yas ⊠ No			

□ No

NDA 21-704 ALLEGRA-D 24 HOUR Extended Release Tablet (fexofenadine HCl 180 mg and pseudoephedrine HCl 240 mg)

	03 12:02PM PATENT LITIGATION-	·	_NO. 5820	P. 4 <sup>-</sup> -
,	For the palent referenced above, provide the following intermetion on the drug sub- use that is the subject of the paneling NDA, amendment, or supplement.	ostanca, drug prod	uci andior method of	}
	2- Drug Substitute (Active Ingradient)	<del></del>		1
	2.1 Does the potent deem the drug substance that is the colors represent to the entry product described in the bending MDA, amen's market, or supplement?	⊠ Yo≠	□ No	1
:	2.2 Does the patient days a drug substance has a different polymorph of the active trigrations described in the penning NDA amonghine, or experience;?	□ Y••	⊠ Ho	

If the anamed to queener 2.2 in "time," to you certify that, as of the date of this declaration, you have tast de domainshaling that a drug product comessing the polymorah will perform the state as the only product described in the NDA? The type of test data required is described at 21 CPR 314,53(b).

2.4 Specify the polymorphic form(s) claimed by the pasent for which you have the last results described in 2.5. Come the pasent claim only a melabolite of the active ingredient pending in the NDA or sup-(Complete the information in section 4 below it the patent claims a ponding method of solin drug product to administer the mesabolite.) ☐ Y → 9 Ø № 2.4 Done the person chain only an informediate? ⊠мь ☐ Yes 2.7 If the patient referenced in 2.1 m a product by precises yearful, at the product olymned in the ore name? (An ensurer is required only if the pullers is a product-by-process palors.) D № **⊠** Y∞ 3. Drug Product (Composition/Formulation) It Does the parent class line crup product, as defined in 21 CFR \$14.8. In the parent NOA. amendment, or evoprement? □ No X Yes 3.2 Core the parent clara only an intermedical? □ v∞ XI No If the petals relatenced in S.Y is a product by process pillars, at the product distinct in the petals review for anything the potent over? (An answer is required only if the potent is a product-by-peccess patent) □ Y≈ Spendars must marrie the intermedian in postion 4 separately for each potent claim deleting a method of using the pending stray product for which approved to being equipit. For each method of use claim referenced, provide the following information:

4.1 Dook the paters claim one or more methods of use for which approved is being sought in the pending MCA, amendment, or supplement? X Yes □ No 4.2 Petami Claim Number (as Relati in the parent) of use not mention approved to being sought in the punding NOA-strumpment, or pupplement?

Substrumpment of pupplements? X Yes 4.28 If the ensurer to 6.2 is

Yes. When't the second of the properties of the second appropriate of the properties of the second of the properties of the second of the s The proposed INDICATIONS AND USAGE are as follows: ALLEGRA-D 24 HOUR Exceeded-Release Tables are indicated for the relief of symptoms suscensed with schomal allergic staintis in adults and chaltren 12 years of age and older. Symptoms trened of footively include amorning, chimorrhos, inchy noscipalistel and/or throst, inchywaterfred eyes, and

ALLEGRA-D 34 HOUR should be administered when both the antibistaminic properties of fexofematine hydrochloride and the massi decongeneant properties of pseudosphedrine hydrochloride are

PORM FDA 3542a (7/\$3)

3. No Relevant Paterns

Best Possible Copy

desired (see CLINICAL PHARMACOLOGY).

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NO. 5820 P. 5

□ Y==

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FORM PDA 3542a (7/03)

DEC. 11. 2003 12:02PM

PATENT LITIGATION-

\_NO. 5820\_\_\_\_P. 6

ansemment, or displanment perjoing under a sensitive palent information in submitted pur this submitted on complies with site requireme is true and correct.	nction 505 of the vulent to 27 CPA rais of the regula	the submission of patent information for the NDA, Pederal Peod, Drug, and Cosmetto Act. This line- 314.53. I steed met I am tradition with 21 CFR 314.53 and than. I visity under penalty of parjury that the foregoing
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nesk applicates box and previde information below.		
☑ NDA Applicent/Holder	⊠ nd Au	M Applicant zhioldor's Allomov, Apert (Representative) or other thorized Official
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Name Charlotte L. Barney Director, Global Patent Litigation	<del></del>	
ADDRES		Céy/Bisig
Avestis Pharmacouricals Inc.		Rridgewater, New Jorsey
1041 Rouse 202-206		·
P.O. Box 6600	<del></del>	Telephone Number
04807-0800		906-331-4551
OSR07-0800 FAX Number (d.:xvalleole)		906-331-4551
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PATENT LITIGATION-

NO. 5820\_\_\_P. 8\_

Notes to Form FDA 3542a for U.S. Patent 5.578,610 for NDA 21-704 (Allegra-D 24 Hour):

Nate to Oversion 2.2. U.S. Patent 5,578,610 claims one of the active ingredients of the drug product Allegra-D 24 Hour (fexofenadine) as a substantially pure compound, and those claims are not limited to specific polymorphic forms. However, the patent does not specifically claim any particular polymorph of the active ingredient fexofenadine, and therefore the answer to Question 2.2 is "no".

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NO. 5820.....

Department of Hoslin and Human Food and Drug Administral PATENT INFORMATION SUBMI	Form Approved: Chill No. 0010-0313 Experience Cours. 27/31/08 See ORM Subprover or Page 2. NOA NO. NOBER				
FILING OF AN NOA, AMENDMENT,	OR SUF	PLEMENT	21-704		
For Each Palent That Claims a D (Active Ingredient), Drug Product ( Composition) and/or Metho	NAME OF APPLICANT / NOA HOLDER A vontise Pharmaconnucis loc.				
The following is provided in accordance with	Section 505	(b) and (c) of the	Federal Food, Drug, and Connetts Act.		
TRADE NAME (OR PROPOSITO TRADE NAME) Allogra-D 24 Hour	<del></del>	<u></u>	<del></del>		
ACTIVE SIGNEDURATES Foundamentine hydrochloride/Pseudoephedrine hydrochl	loride	\$79290734(8) 180mg/240mg			
DOSAZE FORM Tables					
This patent declaration form is required to be such executional, or supplement as required by 21 GFR 314.53. within thirty (30) days either approval of an NAA or say declaration must be submitted pursuent to 21 GFR 31 or supplement. The afformation submysted in the declaration by FDA for liating a patent in the Crange Book.	pplement or 14.58(c)(2)(i) ration form a	within thurty (20) o with all of the re- stamitied upon or a	layer of leaurence of a new patient, it new patient quired information based on the supprovad ND, after approval will be the only information relie		
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Disk code not require a "Yes" or "No" response; places FDA will not lias patient information if you like in patient to not displate far disting.  Por compatient submitted for the pensing HDA foromation described before. If you are not sub- entralists above exciton and sections 5 and 6.  1. GBNBNAL  Limited States Proont Number  0.004-563  d. Name of Parent Corner  Outputics Corp.  1. Hame of business within the United States out instituted to resome notice of opens portfloriou under exciton 905(b)(3) and GRZHBS of the Feating Food. Due, and	attach an administration arresistration arry in the control of the	to patent declara  L or supplantem patents for tide  of Paten.  Plant Owner Three, Rathicz  LS  e Plant, 2 <sup>nd</sup> Ploos n Street  n, Tonola pin Islands  harton  again or representate world Drive	tion or the petent declaration indicates the referenced above, your miset automit all the pending IRDA, programmers, or autoplement in European Dala of Paton.  5/29/2018  FAX Number of explicitles  54-11 4379-4116  G-ball Address (Farehold)  [Solid Address (Farehold)  [Solid Address (Farehold)  [Solid Address (Farehold)  [Solid Address (Farehold)		
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DEC. 11. 2003 12:03PM

PATENT LITIGATION-

-NO. 5820\_\_\_\_P. 10

g. If the patient referenced above has been automated previously for Suing, is the explication

date a new septement date?

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FORM POA 3542a (7/03)

Appears This Way
On Original

Page 2

DEC. 11. 2003 12:03PM

PATENT LITIGATION-

\_NO. 5820\_\_\_\_P. 11

Drug Substance (Active ingradient)		
Does the parent staffs for drug substance that is the policy legisdant in the drug product described in the parking NDA, amendment, or supplement?	☐ Yes	⊠ No
2 Lose the polarif olders a daug substance that is a different polymorph of the active regressions described in the pending NDA, emendment, or supplement?	∐Yes	Ø №
2.3 If the remain to quantion 2.2 is "You," do you easily that, as of the section of this sections on the dispersion, you had comprehense that a drug product contribing the payments and perform the earners in the drug product contribing the payments and perform the earners in the determined in the NSA? The type of test data required is described at 21 CFR 314.53(b).	tive lost data radico	□No
. 4 Specify the polymorphic terrife) etained by the patient (or which you have the last results describ	ned in 2.3.	
5 Does the policing chains only a modulation of the active ingradient pending in the MDA or suppliment (Complete the information in accion 4 bolows if the policin claims a pending method of using the pro-	DenGing	<del></del> ,
drug product to administrat the metabolite.)  2.6 Dobs the parent claim only an intermodula?	☐ Y==	_ <b> </b>
	□ <b>Y</b> ⇔	⊠ No
<ol> <li>If my patent relevanced in 2.1 is a product-by process palent, as the product channel in the parant nower (an interver is required only if the patent is a product-by-process patent)</li> </ol>		□ No
Drug Product (Composition/Formulation)		
.1 Does the peron dairh the drug product, as defined in 21 CFA 314.1, in the conding NOA.		
Amondment, or supplement?  LE Does the patient cases only an informatists?	<u> </u>	□ No
	☐ Y=	<b>⊠</b> N₀
1.3 if the patient retrienced in 2.1 as a product by-process pitters, in the product clarined in the patient never? (An answer is required only if the patient is a product-by-process potent)	□ <b>v</b> ⊷	<b>□</b> **
L. Method of Use		
Sponsors must automit the Internation in acciling 4 separately for each, potent ciples of traduct for which approved to being accigns. For each mathod of use sixth references, provide	sindag 4 method of us the following intermedia	ing the per
<ol> <li>Does the patent death one or shore methods of use servinith approval is being adupts of the panding NDA, emerciment, or supplement.</li> </ol>		<b>13</b> Na
L2 Pagent Court Number (62 fisted in the patent) Does the pasent down interescent in 22 claim of usel for which approved is being sought in the	a pending merced	
APPACATION OF A Community		☐ No
In il the answer to 4.2 is Use: (Supret indicators or memod of use internation as identified ap "Yes," Identify with epitor	MCISCARY IN THE Approved L	opeing)
licity the use with relay- once to the proposed labeling for the drug product.		
koby the use with reference to the proposed in		

FORM FDA 3542± (7/03)

Page 3 bl. objects

5. Deciaration Cartification	
	ar accurate and complete stabulation of patent information for the NOA,
sandifet estart information is assemble	on substrate and porposes summission of present interroperacy or the regio, maker occilion field of the Federal Feod, Drug, and Committe Act. This time- ted purposest to 21 CFR 314.83, I attact that I am familiar with 21 CFR 314.53 and substrates of the regulation, I verify under panelty of parjury that the foregoing
	se statement le a estainal affanse under 18 U.S.C. 1001.
neigenteracing AGN to encorpie bestrone S.A. Indepredet object; (seeinC bestrones adm.	er Poloni Öwner (Alipney, Agent, Representative or
Charlette 1. Browny	izhilos
NOTE: Only on NDA applicatefullar may sub transpris subherland to sign the declaration but n	thing this decimation detectly to the PDA. A patent owner who is not the HDA application to
Chack applicable boy and provide information be	
NOA Applicant/Holder	NOA Applican("effector"; Allomey, Agant (Representative) or other Authorized Official
Patient Clanes	Paterii Owner's Abothey, Aganii (Representative) or Other Authorized Official
Hame Charlotte L. Barney Director, Global Pascas Litigation Address	
Avenus Pharmaceuticals Inc. 164) Ruese 202-200 P.O. Box 6800	Cty/fate Reidpowsser, NJ
21F Code 06607-0500	Telephono Number
FAX Number (Favalety)	. 908-231-4551 E-Meil Address (Favelleble)
906-231-2840	charloochaney#avenis.com
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FORM FDA 3542s (7/03)

Page 4

DEC. 11. 2003 12:03PM ..- PATENT LITIGATION-

NO. 5820—P. 14

		Form Approved, CMB No. 0910-0513		
Food and Drug Administra	Department of Health and Harman Services Food and Drug Admipletration			
PATENT INFORMATION SUBM	ITTED WITH THE	See Chill Sistematic on Page 3 NOA NUMBER		
FILING OF AN NDA, AMENDMENT	T, OR SUPPLEMENT	21-704		
For Each Patent That Claims a l	For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or tilethod of Use			
The following la provided in accordance wis	h Section 500%) and (c) of the C	infant Book Over and Conserve and		
TRADE NAME (ON PROPOSED TRADE NAME) Allogra-D 24 Ruse		and a vote program and		
ACTIVE INCOMEDICATES Fexusemedine hydrochloride/Presiduephedeine hydroch	######################################			
DOSAGE FORM Tablet				
This patent declaration form is required to be visible amendment, or supplement as required by 21 CFR 314.55 Whith minty (30) days after approval of an NDA or a declaration misst be submitted pursuant to 21 CFR 1 or supplement. The information elemented in the dock upon by FDA for fishing a pasent in the Orange Book.  Eact hemoderations or	am the scoress provised in 21 CFR (applement, or within thiny (20) do 114.53(c)(2)(ii) with all of the req efficient form submitted upon or of	314.33(d)(4) ye of leatenne of a now pations, a new potent uned information based on the approved NDA ter approval will be one only information nested		
For hand-written or typewriter varsiums (orsy) of that does not require a "Yes" or "No" response), please	tide report: if additional space i hitsch an udditional page roloron	is required for any namelive enemer (i.e., one oing the question number.		
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DEC. 11. 2003 12:03PM PATENT LITIGATION-

\_\_\_\_\_\_NO. 5820\_\_\_P. 15

For the patiest referenced above, provide the following information as use that is the subject of the people NAA, beardinest, or supplement.	n the drug aubstance, drug pred	ed and/or method of
2. Drug Substance (Active Ingridient)		
2.1 Sees the papers dates the dang substance that is the poster ingredient in the drug described in the parating NDA, amendment, or supplement?		⊠ n•
2.2 Does the petient distrip a only substance that is a different polymerph of the related ingreduct described as the pending NDA, amendment, or autoplement?	□ v••	Ø №ı
2.3 If the american to question 2.3 is "Yes," do you enough this, no of the state of this designmentaling that a child product community the polymonth will perform the same stoomhood in the NDAP The type of must take required is described as 21 CPR 314.	as the drug product	
2.4 Specify the polymorphic formigo channed by the patient for which you have the test		
<u> </u>		
2.9 Does the patiest dawn only a metabolite of size copie supported panding in the NG (Complete the efformation in socion A below If the patient deline a pending meta-	A of supplement?	
and broker in aguitable, she were selected to	□Ym	Ø No
2.4 Doos the palent clern only an intermedials?	□ ves	<b>Ø</b> *•
2.7 If the patient interenced in 2.7 is a product by precises patient, is the product claims patient report (Art shower is inspected only if the patient is a product-by-process pa		□ No
3. Drug Product (Composition/Formulation)		
2.1 Dates the patient claim his drip product, as defend in 21 Crit 314.3, as the punds arrandomers, or subplement?	ng NDA, □ Yee	<b>⊠</b> №
5.3 Does the review about crity an artermediate?	□ Yes	<b>⊠</b> №
3.3 If the patent referenced in 3.1 to a product-by-process potent, in the product claim patent revent? (An entered it required only it the matrix is a product-by-process per	ed in the dent.)	□ No
4. Method of ties		
Systematic must suitable the intermediate to excited 4 superstay for each product for which approved to having excepts. For each reached of use their return	recent, provide the following (aftermake	ning the partiting drug fit:
4.1 Does the polant darm and or more marked of use for which approved is point an the ponding NDA, revendment, or supplement?	🔀 Yes	<b>□</b> №
	ad in 43 claim is panding method ing cought in the punding NDA. X Yee	ΠNα
4.30 If the disease to 4.3 is User (Submit Indicator or method of the information	ne considered the contrasts of the abbusing	

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PATENT LITIGATION ....

\_\_\_\_\_NO. 5820\_\_\_P. 16

Paint Claims generally: A method of treating a historino-mediated condition in a potient having impaired lover function due to disease or due to administration of a constantion drug which inhibits normal liver metabolic function while avoiding cardiac avoors associated with administration of

The proposed INDICATIONS AND USAGE, a relevant section from proposed PRECAUTIONS (Drug Interactions), and a relevant section from proposed CLINICAL PHARMACOLOGY (Spe. is) Populations—Repatically Impaired) are as follows:

#### INDICATIONS AND USACE:

ALLEGRA-D 24 Floor Extended-Release Tables are indicated for the relief of symptome associated with seasonal allergic risinitis in adults and children 12 years of age and older. Symptoms treated effectively include snearing, thinteries, inch nose/palses and/or throat, nohy/wateryfred eyes, and seral confession

ALLEGRA-D 24 HOUR should be adminutered when both the antihistaminic properties of fexalismedine hydrochloride and doesned use CLINICAL PHARMACOLOGY).

#### **PRECAUTIONS**

#### Drug Inscrictions

Pexuternatine hydrochioride and pseudosphedrine hydrochioride do not influence the phurmacukinetics

of each other when administered concerniumdy.

Co-administration of faxofenadine with knoccurations and orythromycin ted to increased plasma tovets of in-administration of imageneous with concentrations and organomycus and to increased plasma severa in textofenadism. Percofenations had no effect on the pharmacolithatics of crystrumycus and kenocutarnis. In two separate slocks, fextofenadise hydrochloride 120 mg twice daily was co-administrated with crystrumycia 500 mg every 6 hours or kemeronaside 400 mg once daily under steady state conditions in normal, healthy volunteers (or 24, each steady). No differences in adverse events or QTc interval were observed when subjects were administered faxofenadism hydrochloride alone or in otherination with crythenmycia or kotroomatule.

The mechanism of these interactions has been evaluated in in vitro, is situ and in vivo animal models. These studies indicate that homeonagole or erythromycia co-administration enhances fessionadine gestrolatestical absurption. In vivo animal studies also suggest that in addition to enhancing absorption, kesocyassole docressos tennienadine gastrointestical socretica, while cryclimmycio may the decrease billary extremen.

the decrease bilitary extreme.

Due to the pseudosphedrine component, ALLEGRAND 23 HOUR is contraindicated in passeurs taking moustaneous carbine component, ALLEGRAND 23 HOUR is contraindicated in passeurs taking moustaneous carbineous carbin should be taken in the administration of ALLEGRA-D 24 HOUR concurnitantly with other sympathominatic amines because combined effects on the cardiovascular system may be harmful to the patient (see WARNINGS).

#### CLINICAL PHARMACOLOGY

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#### Special Populations

Pharmacokinetics in special populations (for rend, hepstic impairment, and age), obtained after a single does of 80 mg feat/formilling hydrochinide, were compared to those from normal volunteers in a separate study of simular design.

Hepatically Impaired. The pharmscokinoids of feroferentine hydrochicusts in subjects with hepatic disease distinct differ substantially from that observed in healthy volumeers. The effect on pseudosephodrine pharmscokinotics is unknown.

5. No Relevent Polente

FORM FOA 3542a (7/03)

Page 3 Nº waterstrand 11

DEC. 11. 2003 12:04PM

PATENT LITIGATION-

NO. 5820\_\_\_\_P. 17

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FORM FOR \$5428 (7/00)

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DEC. 11. 2003 12:04PM PATENT LITIGATION-

\_\_\_\_\_\_NO. 5820\_\_\_P. 20

Food and Daug Administ	Department of Health and Human Services Food and Daug Administration					
PATENT INFORMATION SUBA FILING OF AN NOA, AMENDMEN	MITTED W	ITH THE	See Chill Statement on Page 2.  NOA MUNICIPE			
			31:704			
For Each Palent That Claims a	NAME OF APPLICANT / NOA HOLDER					
(Active Ingredient), Drug Fraduct Composition) and/or Met	Aventus Pharmacousticals Inc					
The following is provided in accordance wi	th Section 500	(b) and (c) of the Fi	ederal Pood, Drug, and Commetic Act			
TRADE NAME FOR PROPOSED TRADE NAMED Allegra-D 24 Hour						
ACTIVE INCAEDIGHT (5)		STRENGTH(S)				
Fexufensdim hydrochloride/Pseudoephourine hydroc	iskeride [	180mg/210mg				
DOSAGE FORM Tables						
This potent declaration form is required to be set amongment, or supplement as required by 21 CPR 314.5 Within shirty (30) days after approval of an NOA or a declaration must be submitted pursuant to 21 CPR or supplement. The information submitted in the doct lapon by PDA for listing a patient in the Crange Book.	u me source supplement, or 314.43(c)(2)(d) kjedon torm si	iprovided to 21 GFR: well in thirty (30) day with all of the requirements ubmitted upon or all	\$14.5%(0)(4), ye of leasurement of it new patent, a now patent frod milormation based on the approved NDA or approved will be the only information rolled			
For hand-written or typewriter versions (only) of that does not require a "Yes" or "No" response), pleas	i Ithia report: i e mizich zn add	f edditional space to dilonal page reference	required for any number enemer (i.e., one the question number.			
PEM will not list patent information it you the patent is not clightle for listing.	an incomplet	e patent declaratio	or the potent declaration indicates the			
For each petert standard for the paneling ADA information described below. If you are not sui complete above pertion and sections 8 and 6.	, amendment besitting any	, or supplement n patents for this p	derenced above, you must submit all the ending NOA, amendment, or susplement,			
1. GENERAL						
a. United States Paters Number 6.187,791	5. tyrus Day 2/13/2001	of Patent	c. Expiration Date of Palent 5/11/2012			
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Canda J. Wille Vice President, Global Patent Litigation	ZiF Code 08907-06U0		FAX Humber (Favelable) 906-231-2691			
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	906-231-572		E-Mail Address (f available)			
. Is the patent referenced above a potent that has been sute	906-231-572	21				

∏ Yes

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ALLEGRA-D 24 HOUR Extended Release Tablet (fexofenadine HCl 180 mg and pseudoephedrine HCl 240 mg)

DEC. 11. 2003 12:04PM ——PATENT LITIGATION \_\_\_\_\_\_NO. 5820\_\_\_P. 21

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FORM FOA 3542a (7/03)

Page 2

DEC. 11. 20	03"12:04PMPATENT LITIGATIONNO. 5820P.	22	
	For the potent referenced above, provide the following infermetion on the drug substance, drug product and/or method of		

For the potent released above, provide are that in the evident of the pending HDA,	the following information on the drug substance amoretment, or supplement.	l, drug produ	jot andler method of
2. Drug Substance (Active Injuridical)			
2.1 Does the potent claim the drug subspance but a described in the parking MDA, emerginees, or	\$upple(nonk <sup>a</sup>		<b>⊠</b> *•
2.2 Date the power date is drug supplanted that is a impresent described in the panding HDA, arrive	a different polymorph of the acabig	☐ Yes	
	orthy that, an of the date of the contention, you have test de	U TAS	Ø №
demonstrating that a circle product concurring the cleans bed in the NDA? The type of test data are	to redeficiely and markered the second as the date received	a □ Yes	□ No
2.4 Sparsty the polymorphic form(s) claimed by the	pelant for which you have the tost moults described to 2.8		
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and begins to standard, the Westpeger)		□ Yes	⊠*•
2.6 Doors the resent claim only an intermediate?		□ Y••	<b>⊠</b> ₩
2.7 If the patent interested in 2.1 is a product by an patent rever? (An answer is required only II the	coase princil, is the product claimed in the Defent is a product-by-process pateric.)	∏ Yes	
3. Drug Product (Composition/Formulation)			
2.1 Does the patent claim the drug product, as definement?	and in 21 CPA 314.1, in the pareting NDA,	□v <sub>=</sub>	⊠ » <sub>0</sub>
2.1 Does the passes claim the drug product, as delin amendment, or supplement?  2.2 Does the patent cause only on intermediate?			
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2.1 Does the passes claim the analy product, as delification of supplement?  2.2 Does the passes claim only in intermediate?  2.3 East passes referenced in 3.1 is a product-by-proposed move? (An answer is required only if the 4. Mostland of Uses  Speciator's mark extend the intermediate in new product for minich appropriat for minich appropriat in being passeds. For	conse paloni, is the predict oblined in the palent is a produce by-predicts paters;)	☐ Yes	⊠ No ⊠ No
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ALLEGRA-D 24 HOUR Extended Release Tablet (fexofenadine HCl 180 mg and pseudoephedrine HCl 240 mg)

DEC. 11. 2003 12:05PM

PATENT LITIGATION-

NO. 5820 P. 23

Patent Claims generally: A method of maning a histometric or historine-volund condition or disease, or providing an antimaterine effect to 1) positive autocopible to possible particle events associated with the administration of serfundine; 2) humans while avoiding the concomitant Habitaty of carries arrythmian associated with the administration of terrecondine; or 3) patients succeptible to QT prolongation and/or vontracular eschyesatia when using torienatine.

The propured INDICATIONS AND USAGE, a relevant sertion from proposed PRECAUTIONS (Drug Intersections), and a relevant section from proposed CLINICAL PHARMACOLOGY (Special Populations—Hopetically Impalsed) are as follows:

#### INDICATIONS AND USAGE

ALLEGRA D 24 How Extended-Release Tablets are indicated for the relief of symptoms associated with seasonal allergic riminis in adults and children 12 years of age and older. Symptoms weated effectively include secreting, riminerises, rich assertables and/or throat, richy/watery/red eyes, and

ALLECINA-D 24 HOUR should be administered whose both the autilitization properties of he hydricideride and the must decompensor properties of presideephedrine hydrochloride are desired (see CLINICAL PHARMACCHOGY)

#### Drug Interactions

Formfeaudine hydracklaride and pseudoophedrine hydrochluride du um influence the pharmacalinetics

of each taker when administered concominantly.

Co-administration of fenolenadine with ketweenszele and arythromycin led to mershad plasms levels of texofensation. Petrofensation had no offeet on the pharmacokineture of crystromycin and tomoreasonie. In two repurse studies, fexofensation bydrochloride 120 mg twice duty was co-administered with erytheromycin 500 mg every 8 hours or knoconszole 400 mg once daily under steady-state creditions to normal, brilliny volunteers (n=24, each study). No differences in adverse events or QTc interval were observed when subjects were administrated fexofenading hydrochloride alone or in combination with crythermycia or iccorporatole.

The nechanism of these mercaclium has been evaluated in in vitra, in any and in vivu animal models. These studies indicate that kereornasole or crythromycin re-administration enhances fexofenedine gastromestical absorption. In vivo saimal studies also suggest that in addition to enhancing aborption, kencountrile docreases fexofenedine gastromestical secretion, while orythromycia may also decrease biliony excretion.

Due to the pseudosphedring component. ALLEGRA-D 24 HOUR is contraindicated in patients taking cooncernment acideste inhibitary and for 14 days after supplying use of an MAO inhibitor, concentually use with aminypericanive drugs which interfers with sympathetic security (eg. methyldope. mocamylamine, and reactine) may reduce their antibyperiensive affects. Increased cotopic processive attivity one occur when pseudoephedrine is used concomitantly with digitalis. Care about the taken in the administration of ALLEGRA-D 24 HOUR concomitantly with other sympathonismetic amines because combined of facts on the cardiovascular system may be harmful to the padent (see WARNINGS).

#### CLINICAL PHARMACOLOGY

#### Special Punulations

Pharmecokinetics in Special populations (for renal, hepaire impairment, and age), obtained after a single tines of 80 mg ferrolenediae hydrochlonde, were exampled to those from normal volunteers in a arparate study of similar design.

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5. No Relevent Palacite

FORM FDA 3542s (7/03)

DEC. 11. 2003 12:05PM---PATENT LITIGATION-

NO. 5820\_\_\_P. 24

For this mending MCA, immendment, or supplement, there are no released passers that claim this drug autonome (author represent), drug proceed passers are considered or method(s) of use, for which the applicant is easiling approved and well respect to which the claim of passers independently and account of the passers of

FORM POA 3642a (7/03)

Page 5

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DEC. 11. 2003 12:05PM

FORM FDA 35424 (7/03)

PATENT LITIGATION - \_\_\_\_\_\_NO. 5820 P. 25

1. The undersigned declares that this is an accurate and complete submilianist of patent information for the MDA, amondment, or supplement parallel under section title of the Polary Epod, Drug, and Controlic No. This time-sumable parallel parallel to 21 CF9 314.82. I speed that I site from this this transmission occupies. This time the parallel parallel of 21 CF9 314.82 and the submitted on complete with 21 CF9 314.83 and the submitted on complete with 21 CF9 314.83 and the submitted on complete with the requirements of the regulation. I verify sender passing of perfuny that the foregoing is true and correct.  Whenhamp: a well-trilly and innovingly false estatement is a criminal attende under 16 U.S.C. 1001.  2 Authorized Signature of NDA applicativitions or Parall Orient (Alterity), Agent, Representative or Date Signed other Authorized Orient Complete to sup the absorbation occupit.  White I Breat Complete to sup the absorbation in wheat is declaration directly to the FDA. A passed overse who is not the NDA application to sup its absorbation of supplication to sup its absorbation of supplication between and provide intervalsion below.    NDA Applicativities are provide intervalsion below.   NDA Applicativities are provide intervalsion below.   NDA Applicativities are provide intervalsion below.   NDA Applicativities are provide intervalsion below.   NDA Applicativities are provide intervalsion below.   NDA Applicativities are provide intervalsion below.   NDA Applicativities are provide intervalsion below.   NDA Applicativities are provide intervalsion of the provide intervalsion below.   NDA Applicativities are provided intervalsion of the provided	Deciaration Cardipostion		•	
Description Signature of NDA Applicantification at Pages Content (Alternary, Agent, Representation or client Authorized Clicketh (Provide Information potent)  CFES Conty on NDA applicantification may submit this declaration directly to the FDA. A petion gener who is not the NDA applicantification is sign the declaration had may not rudomit it directly to the FDA. A petion gener who is not the NDA applicantification is sign the declaration had may not rudomit it directly to FDA. 21 CPR 314.43(c)(4) and (c)(4).  NDA applicantification is sign the declaration hadow.  NDA applicantification is sign the declaration hadow.  NDA applicantification is sign the declaration hadow.  NDA applicantification is sign to the PDA. 21 CPR 314.43(c)(4) and (c)(4).  NOTE Content Declaration is sign to the NDA applicantification of sign of the NDA applicantification is sign to the NDA applicantification is significant and not sign to the NDA applicantification is significant and not sign the behavior and not sign the behavior and not sign the behavior and not sign the product appear is significant and not sign the product application is not sign to the NDA applicantification is significant and not sign the behavior and not sign the behavior and not sign the sign to the NDA applicantification is significant and not sign the sign to the NDA applicantification is significant and not sign the sign to the NDA applicantification is significant and not sign the sign to the NDA applicantification is significant and not sign to the NDA applicantificantificant sign to the NDA applicantificantificantificantificantificantificantifica	surablive patest information is automized put the estimates acompling with the requirem in time and correct. Warning: A withirly and knowingly false out	retien 225 of the Pe retient to 21 CFR 31 httl: Of the regulation invent in a priminal	derel Food, Drug, and Coomedic Act, This little 4.53. I assoc that I am familiar with 21 GPR 314. n. I verify under panelty of perjury dust the fore billenne under 16 U.S.C. 1001.	
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Authorized Others    Palent Ourser   Palent Ourser's Assumery, Agant (Representative) or Other Authorized Official   Palent Ourser's Assumery, Agant (Representative) or Other Authorized Official   Name   Charlotte L. Burgery   Director. Global Patent Litigation     Address   Aventia Pharmacouticals Inc.   If the particle of the particle of the particle of the particle outside of the particle of	ch applicable bes and provide intermation below.			
Name Charlotte L. Burgery Director. Chokal Patoni Litigation Address A versita Phar macousticals Inc. 1041 Route 202-206 P-O. Box 6800 Zif Gode OSEIT-0800  FAX Nambur (# available) 908-231-2540  Talephone Number 908-231-2540  Charlotte, barriery @ available) 908-231-2540  Charlotte, barriery @ available) For partir repressing herein his titu nonfective of information has been examined to seeing 9 hours per response, including the data medical, and completing and removing the collection of information, southing traps data to bush to information, securing the bush to reducing the first covered to the collective of information, excluding registions for reducing the harden to CHR (1979-207) 16(8) Findows Lone Richards MD 20057  An appear, may not remove and appear, and a pagent of any explanation and option of a collection of the collection of the pagent of the collection of information, sections to reducing the burden to CHR (1979-207) 16(8) Findows Lone Richards MD 20057	MDA Applicant folder	NGA A	pticoni sirickier's Attorney, Agent (Representative) or e 20d Official	Place
Charlotte L. Barney Director. Global Patent Utigation Address A vestid Pharmacounicals Inc. 1041 Rouse 202-206 P.O. Box 6800 Zif Code OBS07-0800  FAX Number (P available) 908-231-2551  FAX Number (P available) 908-231-2540  Telephone Humber 908-231-2551  E-thal Address (P available) charlotte, barney & a ventile, cutto between treating replace, data sealor, guillering and mentaning the data accord, and completing and removing the collection of information, sectioning representation of information, sectioning representation of information, sectioning representation of information, sectioning representation of information and Drug Address scales.  Fortil and Drug Address scales.	Paters Duner	☐ Faluri Official	Owner's Astomey, Agent (Reprosentative) or Clinic Auth	Proped
P.O. Box 6500  Zif Code  OBS07-0800  PAX Number (# Beside)  FAX Number (# Beside)  908-231-2551  FAX Number (# Beside)  908-231-2550  Charlotie, berney @ a vontic cum  the partie repressing burden him to the collection of information has been reasonated to nerroge 9 hours per response, including the fame for reviewed  the partie repressing burden him to collection of information in the base reasonated to nerroge 9 hours per response, including the fame for reviewed  the partie of the parties of the collection of information, sectioning and reviewing the collection of information, Section of the parties of the collection of information, sectioning registration of parties of the collection of the collection of information, sectioning registration of the collection of the collec	Charlotte L. Burpey Director. Global Patent Litigation Adoress Avanta Pharmacouticals Inc.		•. •	
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NDA 21-704

ALLEGRA-D 24 HOUR Extended Release Tablet (fexofenadine HCl 180 mg and pseudoephedrine HCl 240 mg)

DEC. 11. 2003 12:05PM ....PATENT LITIGATION-

\_\_\_\_\_NO. 5820\_\_\_\_P. 27

Department of Hastin and Human Food and Orug Administra			Form Apparent Chill No. 0910-0613 Explaint Date: 07/37/76 East Chill Statement on Page S.		
PATENT INFORMATION SUBMI FILING OF AN NDA. AMENDMENT			NDA MUNISER		
	•		21-704		
For Each Palent That Claims a D			HAME OF APPLICANT / NOA HOLDER Avends Pheressociaticals Inc.		
(Active Ingradiant), Drug Product Composition) and/or Meth		n <b>a</b> nd	VANDER Link discondent lies		
The following in provided in apportunce with	Section 3060	) and (c) of the ?	ederal Pood, Drug, and Cosmetic Act.		
TRADE HAME FOR PROPOSED TRADE HAME) Allegra-D 24 lines		·			
ACTIVE INCREDIGNESS	1 5	THENGTHES)			
Fexionadine hydrochloride/Tecndusphedeine hydroch	kride !	80mg/240mg			
BORAGE POPAM Tables					
This patent disclaration form in required to be sell amondment, or supplement as required by 21 CFR 31s.23 Within thing City days wher approved of an NOA or in destruction must be automated pursuant to 21 CFR 3 or supplement. The information automated in the dock upon by FDA for listing a patent in the Orange Book.			414 62/4/41		
For hand-written or typewriter versions (enly) of that door not require a "Yes" or "No" response), please	tisis report: If	additional apace	is required for any narrativo ensurer (i.e., one		
PDA will not list potent information if you the a patent in not eligible for listing.	n incomplete	petent declarati	on or the estem declaration indicates the		
For each patent submitted for the penning ICAL information described below. If you are not suit sumplets above section and eaching 5 and 6.	amendment, milling any p	or supplement i userity for this	eferenced above, you must everall all the pending NDA, emendment, or expolement,		
1. GENERAL					
a. United States Patient Humber 6.399.632	5- leave Date of 6/4/2003	ri Patieni	c. Explinition Date of Patern 7/11/2011		
d. Name of Patient Owner	Address to Pa		<del></del>		
Cardern Capital J.P.	c/o Wenbrok				
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Louis J. Wille Vice President, Global Patent Languages	289 Octo 08907-0800		903-231-3691		
- '	Totaphore Nur 908-231-572		E-Mail Address (# evelenis) lou.wille@avenis.com		
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<ol> <li>to the patent coloratoed above a patent that have been submapproved NOA or supplement referenced appive?</li> </ol>	1	-	□ Ver ⊠ No		

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PATENT LITIGATION-

NO. 5820<u>P.</u> 28

. If the patient referenced above has been submidded pro-toubly for lasting is the depth days

date a new anythetecon class?

Yes 
No

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PORM FDA 3542a (7/03)

Page 2

DEC. 11. 2003 12:06PM

PATENT LITIGATION-

NO.

58		

For the potent referenced shows, provide the following information on the drug substance too that is the subject of the pending NDA, amendment, or supplement.	s, drug prod	ual and/or method
8. Drug Substance (Active Ingressions)		
2.1 Dues he passer claim the drug substance that is the policy ingredient in the drug product described in the passers NCA, environment, or supplement?	□ Yes	⊠ No
2.2 Does the patent chain a steep subspaces that it is different polymorph of the notive improduct department in the parting NDA, constrainent, or outplaces;	☐ Yee	⊠ No
2.3 If the anomar to question 2.3 in "Yes," do you contry this, as of the date of the declaration, you have not a demonstrating that a daug product containing the polymorph will perform the same as like drug product containing the polymorph will perform the same as like drug product described in the MDAT The type of sext data required in dracticed at 21 CPR 314 S3(s).	☐ Yes	□ No
2.6 Specify the polymounile location claimed by the pater's for which you have the lest recide described in 2.3.	<del></del>	<u> </u>
2.8 Does the pasters offers only a street build of the active ingredient paneling to the HDA or supplement? (Complete the advantage of using the below 4 the patent claums a pending method of using the pending drug product in administer one manifolds []	<u> </u>	
LS Open the present claim only an intermediate?	□ Yes	 ⊠ No
2.7 If the passeri referenced in 2.1 is a product-by-process passeri, in the product commed in the passeri nover? (An extense is required only if the paters in a product-by-process passer?)	□ Y#	
1. Drug Product (Composition/Formulation)		
1.1 Dans the paper claim the drug product, as plained in \$1 CFR 314.3, or the pending NDA, assortiment, or supplement?  1.2 Dans the patent often only an informatique?	<b>□</b> 700	<b>2</b> %
	Yes	Ø re
1.3 If the patient referenced in 1.1 is a product day process patient, in the product charged in the patient report? (An prover is required only II the patient r; a product-by-process belant.)	□ ves	□ No
4. Method of Use		
Sponeurs steel outline the Intermetion is section 4 superably for each patent claim stateling a product for solids approved to being sought, for each method of use older referenced, provide the follow	method of up	ing the panding do
1) Does the patent clath one or exce metrode of use for vetoff approval is being sought in the pending NDA, amendment, or expression:	⊠ Yas	<b>□</b> ‰
1.2. Palent Chain Number (for street in the peears)  Does the puters clean inferenced in 4.2 claim a pending of uses for which approved to being sought in the pending arrangement, or supplied by the period of the pending arrangement, or supplied in the pending arrangement are supplied in the pending arrangement are supplied in the pending are supplied in the pendi	method NDA.	
Can if the artempt to California (Submit addressed to tenting of the Committee of the Commi	🖄 Yos	[] <del>No</del>

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PATENT LITIGATION .....

NO. 5820\_\_\_P. 30

You," identify with specificity that use with refer anose to the propessed labeling for the drug product.

Phone Chimz generally: A method of treating a histograms-mailured condition or providing/theorizing an autihus/service effect in a 1) a patient in whom serfenadore is not metabolized at the retends face to the terfenadine sold sectabolite, while avoiding the concognitude liability of cariatic anythmias associated with the administration of terfenadore (2) a patient in whom serfenadine is not metabolized at the mortral rate to the terfenadine acid everabolite; 3) a patient in whom serfenadine is not metabolized in the mortral rate to the terfenadore acid everabolite; 3) a patient in whom serfenadine and arrive terfenadore acid everabolites and who is subject to UT prolongation and/or veneralize tactyon-that when being excluding or 4) a human who also received a product which intuities terfenadore rectabolism.

The proposed INDICATIONS AND USAGE, a relevant section from proposed PRECATTICES (Drug Instructions), and a relevant socilian from proposed CLINICAL PHARMALYMING (Special Propulations—Hopelically impaired) are as follows:

#### INDICATIONS AND USAGE

ALLIGRA-D 24 Hour Exended-Release Tablos are indicated for the relief of symptoms assuciated with sassonal aftergic relievis in adults and children 12 years of age and older. Symptoms treated effectively include encoring, remorrhed, tech governable and/or throat, include encoring, remorrhed, tech governable and/or throat, includes another dependent.

ALLEGRA-D 24 (FOUR should be administered when both the smith eastline properties of fexolenative hydrochlatide and the navel decompanies properties of pseudosphedisine hydrochlatide are destred (see CLINICAL PHARMACOLOGY).

#### PRECAUTIONS

Drug Interaction

Peroferadine hydrochloride and pseudocphodrine hydrochloride do not influence the pharmacricinaries of each other when administrate concomitantly.

Co-administration of incoferacine with honocomicals and erythronyem had to increased planta levels of

Co-administration of fearinatine with kennopsizate and cryshromyom had to increased planes levels of fearinandine. Fearinadine had no effect on the pharmacochimstics of crythromyoth and kennopsiste. In two expanse audies, fearifending hydrochloride 130 mg whos daily was co-administered with crythromyoto 500 mg every 8 hours or kennopsiste 400 mg once daily under steady-state conditions to normal, healthy submoore (see2s, each study). No differences in educate events or QTo interval were otherwed when subjects were administered fexofenation hydrochloride slune or in combination with crythromyotic or ketocoagande.

The mechanism of them instructions has been avaluated in the viru, in situ and in vivo animal models. These studies indicate that tenconezole or stythologycla co-administration enhances least-fonding gasteristicalism absorption. In vivo seignoi studies also suggest that is addition to enhancing absorption, ketnonezole decreases fearfereading gasteristicalisal secretion, while crystromycla may also decrease billing exension.

Due to the pseudocphodific compunent, ALLEGRA-D 24 HOUR is contraindicated in potents taking monomine exidute inhibitors and for 14 days ofter morphing use of an MAO inhibitor. Concominant we with antito-percentive drugs which interfore with sympathetic activity for, methyldopa, metamylardine, and reserpine) may reduce their authypotential to effects. Togressed coupie pacemakes activity can occur when pseudosphedrine is used concominantly with digitalis. Care should be taken in the administration of ALLEGRA-D 24 HOUR ornormization with other sympatheminatic atmost because combined effects on the tarditorascular system may be humbled to the patient (see WARNINGS).

#### CLINICAL PHARMACOLOGY

Special Populations

Phermacokinetics in special populations (for renal, hopatic impairment, and age), obtained after a single does of 80 mg festoferadine hydrochloride, were dempared to those from normal volunteers in a separate study of similar design.

Hepatically Impaired. The pharmacokineties of fexofenadine hydrochloride in subjects with hepatic disease fild not differ substantially from that observed in healthy volumeers. The effect on pseudosephedrine pharmacykinesies is unknown.

FORM FDA 3542# (7/02)

Page 4

DEC. 11. 2003 12:06PM

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NO. 5820\_\_\_\_P. 31

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PATENT LITIGATION ....

NO. 5820\_\_\_P. 32

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The undersigned declarate that this is an assument, or supplement perioding under sensitive patent information is authitited putties with the inquirement authorities and correct.  Warning: A William and knowingly taken state.	note of the regulation. I verify	under penalty of perfusy that she feregoing
Authorized Signature of NOA Applicant/Holder or Pass other Authorized Officiell (Frontile Information below)	IN Dense (Adventy Angel Benne	
Chalthe L. Barry		12/4/03
Tig: Only in NGA applicantification may submit U for is extracted to sign the declaration but may re-	nic declaration discoly to the Fit t submit it directly to FDA, 21 CFS	DA, A patent owner who is not the NDA appli 1914.59(4)(4) and (4)(4).
ich spolicable best and provide informacion bejoer.	·	
NDA Applican#Holder     NDA Applican#Holder	NOA Applicant of Authorized Official	older's Atlanney, Agent (Representative) or other
Passet Owner	Palent Center's As	lotroy, Agent (Represensive) or Other Authorized
Name Charkete L. Barney Director, Global Parent Literation		
Avents Phermiceniculs Inc. 1041 Reuse 202-206 P.O. Box 6800	ChySmin Bridgewater	, New Jessey
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## Amended Certification Pursuant to 21 Sec. C.F.R. 314.50(i)(6)

### Paragraph IV Certification

Pursuant to 21 U.S.C. Sec. 355(b)(2)(A)(iv), 21 CFR Sec. 314.50(i)(1)(i)(A)(4), and 21 CFR Sec. 314.50(i)(3), Aventis Pharmaceuticals, Inc. certifies that Patent Number 4801461 will not be infringed by the manufacture, use or sale of Allegra-D® 24 Hour (fexofenadine HCl 180mg/pseudoephedrine HCl 240 mg) Extended Release Tablets, for which this application is submitted. The patent owner, ALZA Corporation, has granted Aventis Pharmaceuticals, Inc. a patent license.

Authorized signature of attorney, agent, representative or authorized official

Date - October 12, 2004

Charlotte L. Barney Director, Global Patent Litigation

Aventis Pharmaceuticals, Inc. 1041 Route 202-206 P.O. Box 6800 Bridgewater, NJ 08807-0800

Telephone Number 908-231-4551

# Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

\_\_\_\_ § 552(b)(5) Deliberative Process

\_\_\_\_\_ § 552(b)(5) Draft Labeling



October 12, 2004

Badrul Chowdhury, M.D., Ph.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Drug Products (HFD-570)
Central Document Room
5901-B Ammendale Road
Beltsville, Maryland 20705

# NDA 21-704 ALLEGRA-D 24 HOUR™ Extended Release Tablets AMENDMENT TO PENDING APPLICATION Amendment 07: Patent Certification

Dear Dr. Chowdhury:

Reference is made to NDA 21-704 ALLEGRA-D 24 HOUR<sup>TM</sup> Extended-Release Tablets (fexofenadine hydrochloride 180mg and pseudoephedrine hydrochloride 240mg) submitted to the Agency on December 19, 2003 and currently under review with a PDUFA action goal date of October 19, 2004.

The enclosed Amendment 07 to this pending application contains information for Item 14, Patent Certification. Pursuant to 21 CFR §314.50(i)(6), Aventis Pharmaceuticals, Inc. ("Aventis") hereby notifies the Agency that the above referenced application is amended to change the certification previously provided under Section 505(b)(2)(A) from Paragraph III to Paragraph IV. ALZA Corporation ("Alza"), the owner of Patent No. 4801461, has granted Aventis a license for ALLEGRA-D 24 HOUR<sup>TM</sup> Extended-Release Tablets (fexofenadine hydrochloride 180mg and pseudoephedrine hydrochloride 240mg). Included with this amendment (Patent Information, Item 13) is Alza's consent to an immediate effective date upon approval of this NDA.

NDA 21-704 was submitted with an electronic archival copy (e-NDA) in accordance with current guidance for electronic submissions according to Form 356h NDA format. In compliance with that guidance, the enclosed Amendment is also submitted with an electronic archival copy.

Aventis Pharmaceuticals, Inc.
NDA 21-704 Amendment 07 (ALLEGRA-D 24 HOUR™ Extended Release Tablet)
October 12, 2004
Page 2

Aventis considers the information included in this submission to be confidential and proprietary, and requests that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Aventis according to CFR §314.430.

On behalf of Aventis, we look forward to continuing to work with the Division to facilitate the review of this application. If you have any questions or need additional information during the review, please contact the undersigned, Kimberly S. Stranick, Ph.D., at (908) 304 6580 or, in my absence, Eric A. Floyd, Ph.D., at (908) 231 2474.

Sincerely, Kunherly Stranick

Kimberly S. Stranick, Ph.D.

Director, Regulatory Liaison US Regulatory Affairs

Attachment

Enclosures:

Electronic archival copy: 1 CD-ROM labeled NDA 21-704 ALLEGRA-D 24 HOURTM Extended Release Tablets, Amendment to Pending Application, Amendment 07 October 12, 2004, CMC 1 paper copy of Cover Letter, Form FDA356h and Item 14 with original signatures

cc: Ms. Christine Yu, Regulatory Project Manager

Aventis Pharmaceuticals, Inc.
NDA 21-704 Amendment 07 (ALLEGRA-D 24 HOUR™ Extended Release Tablet)
October 12, 2004
Page 3

NDA 21-704 Electronic Submission Information

Description Format (Electronic/Paper)

Item	Description	Electronic	Paper
	Cover Memo	X	X
	Form 356h	X	X
ī	Index	X	
2	Labeling		
3	Application Summary		
4	Chemistry		
5	Nonclinical Pharmacology & Toxicology		
6	Human Pharmacokinetics and Bioavailability		
7	Clinical Microbiology		
8	Clinical		
9	Safety update report		
10	Statistical		
11	Case Report Tabulations		
12	Case Report Forms		
13	Patent Information	X	
14	Patent Certification	X	X
15	Establishment Description		
16	Debarment Certification		
17	Field Copy Certification		
18	User Fee Cover Sheet		
19	Financial Information		
20	Other		

#### **Electronic Submission Summary**

Media Type and Number:

1 CD-ROM

File Formats:

Portable Document Format (.pdf)

Total Size:

Electronic Submission - approximately 1 MB

#### Virus Verification:

Aventis certifies that all electronic media are free from computer virus. The virus scan was performed using Symantec's Norton Antivirus Corporate Edition, Program Version 7.50.846, Scan Engine Version 4.1.0.6. The Virus Definition File is Version 61006t, issued October 6, 2004.

#### **Sponsor Contact:**

Regulatory Affairs

Kimberly S. Stranick, Ph.D. Director, Regulatory Liaison US Regulatory Affairs Aventis Pharmaceuticals, Inc. 908 304 6580 908 812 9270 mobile 908 304 6317 fax

EXCLUSIVITY SUMMARY FOR NDA # 21-704 SUPPL #
Trade Name Generic Name  Allegra-D 24 Hour ER Tablet  (fexofenadine HCl 180 mg/pseudoephedrine HCl 240mg)
Applicant Name Aventis Pharmaceuticals HFD # HFD-570
Approval Date If Known10/19/04
PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?
1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.
a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement? YES $/\underline{\checkmark}$ / NO $/$ /
If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8
505b2
c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")
YES // NO /_ <u>\</u> /
If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.
Aventis conducted two PK studies to support this
NDA, but they also monitored safety endpoints, such as
AE's, vital signs, physical exams, clinical labs, ECG's.
If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?
YES // NO /_ <u>\left\</u> /
If the answer to (d) is "yes," how many years of exclusivity did the applicant request?
e) Has pediatric exclusivity been granted for this Active Moiety?
YES // NO //
If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Writen Request?
<u>No</u>
IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.
2. Is this drug product or indication a DESI upgrade?
YES // NO /_ <u>\forall/</u>
IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).
PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)
1. Single active ingredient product.
Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved.

Ans	wer	"no	'if	the	comp	oun	d requires	metal	ooli	ic c	onvers	ion	(other
tha	n de	este	rifi	catio	n of	an	esterified	form	of	the	drug)	to	produce
an	alre	eady	appr	coved	acti	ve	moiety.				_		_

	•	YES / /	NO / /	
If "yes," identify	the approved	drug product(s)	containing	the
active moiety, and,	if known, the	NDA $\#(s)$ .	_	

	NDA#	 		
NDA#	NDA#			

# 2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one neverbefore-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-021 Efidac 24(pseudoephedrine HCl) ER tablet

NDA# 20-625 Allegra (fexofenadine HCl) capsule

NDA# 20-872 Allegra 30, 60, 180 mg (fexofenadine HCl) tablets

NDA# 20-786 Allegra-D ER (fexofenadine 60mg/PSE 120mg) tablet

Others...

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES" GO TO PART III.

#### PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /\_\_/ NO /\_\_\_/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

- 2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.
  - (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /\_\_\_/ NO / /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?
YES // NO // (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.
YES // NO //
If yes, explain:
(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?
YES // NO //
If yes, explain:
(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this

section.

- 3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.
  - a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /\_✓\_/ NO /\_\_/

Investigation #2 YES /\_✓\_/ NO /\_\_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

Study M106455B/3081 NDA 20-872

Study PJPR0027 NDA 20-872

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /\_\_/ NO /\_✓\_/

Investigation #2 YES /\_\_/ NO / $\underline{\checkmark}$ \_/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

	c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):
esse the the inve the its stud	To be eligible for exclusivity, a new investigation that is ential to approval must also have been conducted or sponsored by applicant. An investigation was "conducted or sponsored by" applicant if, before or during the conduct of the estigation, 1) the applicant was the sponsor of the IND named in form FDA 1571 filed with the Agency, or 2) the applicant (or predecessor in interest) provided substantial support for the dy. Ordinarily, substantial support will mean providing 50 cent or more of the cost of the study.
	a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?
IND	<pre>Investigation #1  # YES // ! NO // Explain:! !</pre>
IND	Investigation #2 ! ! ! ! ! ! ! ! ! ! ! ! ! ! ! ! ! !
	(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?
	Investigation #1 !
	YES // Explain! NO // Explain!

! ! Investigation #2 !	
YES // Explain!	NO // Explain
there other reasons to bell be credited with having "o (Purchased studies may exclusivity. However, if a (not just studies on the considered to have spon	swer of "yes" to (a) or (b), as ieve that the applicant should no conducted or sponsored" the study not be used as the basis for all rights to the drug are purchase the drug), the applicant may be sored or conducted the studie its predecessor in interest.)
	YES // NO //
If yes, explain:	
stine Yu, R.Ph. atory Project Manager	Date
	Date
l A. Chowdhury tor, Division of Pulmonary	

Form OGD-011347 Revised 05/10/2004

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Badrul Chowdhury 10/20/04 02:29:00 PM



# **Debarment Certification**

December 1, 2003

Aventis Pharmaceuticals, Inc. hereby certifies that it has not used and will not use in any capacity the services of any person debarred pursuant to section 306(a) and (b) of the Federal Food, Drug and Cosmetic Act [21 U.S.C. 335(a) and (b)] in connection with this application.

Steve Caffé, M.D.

Vice President, Head US Regulatory Affairs Tel (908) 231 5863 or (908) 304 6580

Enir A. Flyd for S.C.

19. FINANCIAL INFORMATION FOR INVESTIGATORS

Appears This Way On Original ALLEGRA-D 24 HOUR Extended Release Tablet (fexofenadine HCl 180 mg and pseudoephedrine HCl 240 mg)

DEPARTMENT OF HEALTH AND HUMAN SERVICES Food and Drug Administration Form Approved: OMB No. 0910-0396 Expiration Date: February 28, 2006.

# CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

#### TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

igators	Dennis N. Morrison, D.O. Investigator, S/1001, S/1002	·Ľ	
d invest	Γ 7		
Clinica	C 3		

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

a. a.u.u.a. 1	TITLE Vice President, Head US Regulatory Affairs
FIRM/ORGANIZATION Aventis Pharmaceuticals, Inc.	
SIGNATURE (in d. Atry) for	J. C. 12/01/2003

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and muintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services Food and Drug Administration 5600 Fishers Lane, Room 14C-03 Rockville, MD 20857

# NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

			mpopulating		
Original NDA 21-704	Efficacy Supplement Type SE-		Supplement Number		
Drug: Allegra-D 24 Hour ER tablet (Fexofenadine HCl 180mg/PSE HCl 240mg)			Applicant: Aventis Pharmaceuticals, Inc		
RPM: Christine Yu, R.	Ph.		HFD-570	Phone # 301-827-1051	
Application Type: () 505(b)(1) ( ) 505(b)(2)  (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)			d drug(s) referred to in 505(b)(2 (s)):	) application (NDA #(s), Drug	
If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review.  Please update any information (including patent certification information) that is no longer correct.					
(✓) Confirmed and/or	corrected				
Application Classif	fications:	·	9		
<ul> <li>Review pr</li> </ul>	iority		(1	() Standard () Priority	
Chem class	ss (NDAs only)		3		
• Other (e.g	., orphan, OTC)		The second secon		
User Fee Goal Date	es		О	ctober 19, 2004	
Special programs (indicate all that apply)				( ) None subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ) Fast Track ) Rolling Review ) CMA Pilot 1 ) CMA Pilot 2	
User Fee Information	on				
User Fee	Supplement fee agreed upon by Age	ncy		Paid UF ID number 4443	
User Fee waiver				Small business Public health Barrier-to-Innovation Other (specify)	
• User Fee e	xception	entre est les ests.	C	Orphan designation No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) Other (specify)	
Application Integrit	y Policy (AIP)				
	is on the AIP	11 1111 4 - 1 44 -	()	Yes (✓) No	

<ul> <li>Exception for review (Center Director's memo)</li> <li>OC clearance for approval</li> <li>Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification &amp; certifications from foreign applicants are cosigned by US agent.</li> <li>Patent</li> <li>Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.</li> <li>Patent certification [505(b)(2) applications]: Verify that a certification was</li> <li>21 CFR 314.50(i)(1)(f)</li> </ul>	i)(A)
<ul> <li>Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification &amp; certifications from foreign applicants are cosigned by US agent.</li> <li>Patent</li> <li>Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.</li> </ul>	i)(A)
not used in certification & certifications from foreign applicants are cosigned by US agent.  Patent  Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.  (✓) Verified	i)(A)
<ul> <li>◆ Patent</li> <li>• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.</li> </ul>	<i>î</i> )(A)
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. (✓) Verified	i)(A)
the drug for which approval is sought.	<i>i</i> )(A)
Detent continued in 1505/h/(2) conflictional, Varies that a continue was 21 CED 214.50(i)(1)(i)	î)(A)
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.  21 CFR 314.50(i)(1)(i) (i) (ii) (iii) (ii	
21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)	
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). (If the application does not include any paragraph IV certifications; mark "N/A" and skip to the next box below (Exclusivity)).	certification)
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.	
Answer the following questions for each paragraph IV certification:	
(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? () Yes (✓) No	
(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).	
If "Yes," skip to question (4) below. If "No," continue with question (2).	
<ul> <li>(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?</li> </ul>	
If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).	
If "No," continue with question (3).	
(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below. (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) () Yes () No submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity). If "No," continue with question (5). (5) Did the patent owner, its representative, or the exclusive patent licensee () Yes () No bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity). If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)	
<ul> <li>Exclusivity summary</li> <li>Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</li> </ul>	No
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.	() Yes, Application #( ✓) No
Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	9/10/04

200 July 100 100 100 100 100 100 100 100 100 10	
Actions	
Proposed action	(✓) AP () TA () AE () NA
Previous actions (specify type and date for each action taken)	
Status of advertising (approvals only)	<ul><li>(✓) Materials requested in AP letter</li><li>() Reviewed for Subpart H</li></ul>
❖ Public communications	
Press Office notified of action (approval only) will do after approval	(✓) Yes () Not applicable
Indicate what types (if any) of information dissemination are anticipated	<ul> <li>( ) None</li> <li>( ) Press Release</li> <li>( ) Talk Paper</li> <li>( ) Dear Health Care Professional Letter</li> </ul>
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
Division's proposed labeling (only if generated after latest applicant submission of labeling)	10/18/04
Most recent applicant-proposed labeling	10/13/04
Original applicant-proposed labeling	12/19/03
Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	DMETS- 7/1/2004
Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	en e
Division proposed (only if generated after latest applicant submission)	
Applicant proposed	9/29/04
• Reviews	DMETS- 7/1/2004 See each discipline review
❖ Post-marketing commitments	See eden discipline review
Agency request for post-marketing commitments	
Documentation of discussions and/or agreements relating to post-marketing commitments	
<ul> <li>Outgoing correspondence (i.e., letters, E-mails, faxes)</li> </ul>	<b>✓</b>
❖ Memoranda and Telecons	None
❖ Minutes of Meetings	
EOP2 meeting (indicate date)	1/29/02 under IND 48,486
Pre-NDA meeting (indicate date)	8/27/03 under IND 66,289
<ul> <li>Pre-Approval Safety Conference (indicate date; approvals only)</li> </ul>	
Other	
❖ Advisory Committee Meeting	
Date of Meeting	The second secon
48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	

Microbiology (efficacy) review(s) (indicate date for each review)  Safety Update review(s) (indicate date or location if incorporated in another review)  Pediatric Page(separate page for each indication addressing status of all age groups)  Demographic Worksheet (NME approvals only)  Statistical review(s) (indicate date for each review)  Biopharmaceutical review(s) (indicate date for each review)  Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)  Clinical Inspection Review Summary (DSI)  Clinical Inspection Review Summary (DSI)  CMC review(s) (indicate date for each review)  Review & FONSI (indicate date of review)  Review & Environmental Impact Statement (indicate date of each review)  Acceptable 10/4/04  Pacilities inspection (provide EER report)  Methods validation Will not be requested see CMC review page 98  Pharm'tox review(s), including referenced IND reviews (indicate date for each review)  Nonclinical inspection review summary  Statistical review(s) of carcinogenicity studies (indicate date for each review)		Sentence approximation for the	
<ul> <li>Clinical review(s) (indicate date for each review)</li> <li>Microbiology (efficacy) review(s) (indicate date for each review)</li> <li>Safety Update review(s) (indicate date or location if incorporated in another review)</li> <li>Risk Management Plan review(s) (indicate date/location if incorporated in another review)</li> <li>Pediatric Page(separate page for each indication addressing status of all age groups)</li> <li>Demographic Worksheet (NME approvals only)</li> <li>Statistical review(s) (indicate date for each review)</li> <li>Statistical review(s) (indicate date for each review)</li> <li>Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)</li> <li>Clinical Inspection Review Summary (DSI)         <ul> <li>Clinical Inspection Review Summary (DSI)</li> <li>Clinical Studies</li> <li>Bioequivalence studies</li> </ul> </li> <li>CMC review(s) (indicate date for each review)</li> <li>CMC review(s) (indicate date for each review)</li> <li>Categorical Exclusion (indicate review date)         <ul> <li>Review &amp; FONSI (indicate date of review)</li> <li>Review &amp; Environmental Impact Statement (indicate date of each review)</li> </ul> </li> <li>Microbiology (validation of sterilization &amp; product sterility) review(s) (indicate date for each review)</li> <li>Microbiology (validation of sterilization &amp; product sterility) review(s) (indicate date for each review)</li> <li>Methods validation Will not be requested see CMC review page 98</li> <li>Methods validation Will not be requested see CMC review page 98</li> <li>Pharm'tox review(s), including referenced IND reviews (indicate date for each review)</li> <li>Nonclinical inspection review summary</li> <li>Statistical review(s) of carcinogenicity studies (indicate date for each review)</li> <li>Categorical Review(s) of carcinogenicity studies (indica</li></ul>			
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# Appendix A to NDA/Efficacy Supplement Action Package Checklist

an application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

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§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

\_\_\_\_\_ § 552(b)(5) Draft Labeling

#### **DIVISION DIRECTOR'S MEMORANDUM**

Date:

October 19, 2004

To:

NDA 21-704

From:

Badrul A. Chowdhury, MD, PhD

Director, Division of Pulmonary and Allergy Drug products, HFD-570

Product:

Allegra-D 24 Hour (fexofenadine HCl 180 mg and pseudoephedrine HCl

240 mg) Extended-Release Tablets

Applicant:

Aventis Pharmaceuticals, Inc.

#### Administrative and Introduction

Aventis Pharmaceuticals submitted NDA 21-704 for Allegra-D 24 Hour (fexofenadine HCl 180 mg and pseudoephedrine HCl 240 mg) Extended-Release Tablets on December 19, 2003. The PDUFA due date on this application is October 19, 2004. Allegra-D 24 Hour Tablets is proposed for prescription use in patients 12 years of age and older for relief from symptoms of seasonal allergic rhinitis. The product is particularly intended to be used when both the antihistaminic properties of fexofenadine and the nasal decongestant properties of pseudoephedrine are desired. The proposed dose is one tablet once a day. Aventis has three products containing fexofenadine approved for marketing in United States. These are Allegra Capsules (fexofenadine HCl 60 mg, NDA 20-625), Allegra Tablets (fexofenadine HCl 30 mg, 60 mg, and 180 mg, NDA 20-872), and Allegra D Tablets (fexofenadine HCl 60 mg and pseudoephedrine HCl 120 mg, NDA 20-786). The currently marketed Allegra D product is dosed twice daily. Since fexofenadine and pseudoephedrine are both approved marketed products, no clinical efficacy or safety studies were required. The clinical program for this application consists of bioequivalence studies with supported safety data. Aventis also included summaries of two clinical studies that were previously submitted to NDA 20-872 to further support this application. The submitted clinical data support approval of this application. Although there are no outstanding issues from any disciplines that would preclude approval of this application, Aventis informed the Division on September 22, 2004, of significant manufacturing process changes that would require approval of a prior approval CMC supplement before Aventis can market products manufactured with the new process.

Aventis Pharmaceuticals originally submitted this NDA as a 505(b)(1) application. However, because Aventis does not have ownership of the data for extended-release pseudoephedrine, this NDA should have been submitted as a 505(b)(2) application. The Division notified Aventis, and Aventis amended the NDA on February 17, 2004, to a 505(b)(2) application with initial Paragraph 2 and 3 certifications, followed by Paragraph 4 certification on October 12, 2004. Aventis has entered into a licensing agreement with the owner of the extended-release pseudoephedrine data (ALZA Corporation) and has

submitted appropriate patent certification to the Agency. Aventis has submitted a letter to the NDA from ALZA which states "ALZA does not intend to file an action for patent infringement against Aventis or its affiliates or sublicensees" based on a claim of patent infringement. "Further, ALZA consents to FDA's approval of Aventis' 505(b)(2) application for Allegra-D 24 Hour with an immediate effective date on or after the date of this letter." Virginia Beakes of the Office of Regulatory Policy has checked with the Office of Chief Council and has informed the Division that this NDA may be approved from a regulatory standpoint.

Chemistry, Manufacturing, and Controls, and Establishment Evaluation	
Allegra-D 24 Hour contains active drug substances pseudoephedrine in a sustained	
release and fexofenadine HCl in an immediate release outer coat, and a	
number of commonly used excipients. The L I which contains L	
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the control release of pseudoephedrine via a well known L J mechanism.	
Fexofenadine HCl drug substance is produced by Aventis and pseudoephedrine HCl drug	
substance is produced by $\subset$	
J are manufactured at a site in C	
3 all subsequent manufacturing and packaging are performed at	
Aventis site in Kansas City. All manufacturing sites related to this application have	
acceptable evaluation status.	
-	

On September 22, 2004, Aventis informed the Division that they have installed new equipment  $\Box$  that has affected the dissolution profiles of the tablets. This is a substantial change and would require data to link the tablets manufactured with the new equipment to the tablets manufactured with the old equipment that was originally submitted for Agency review. Other than this major issue, there were some minor CMC issues that were resolved during review of the application. There are also some minor deficiencies that will not impact the safety or efficacy of the drug product, which the applicant has agreed to resolve post-approval. These are discussed in detail in Dr. Jao's excellent review. The CMC team has recommended an approval action on this application, and I concur with that recommendation. This recommendation is for the drug product produced with the original equipment that was submitted to the Agency and was fully reviewed. Aventis will need to submit a pre-approval supplement before they can market products manufactured with the new equipment.

# Clinical Pharmacology and Biopharmaceutics, and Clinical

The applicant submitted results of three clinical pharmacology studies and a summary of safety data. Of the three clinical pharmacology studies two were conducted with the to-be-marketed formulation and were considered relevant to this NDA. The two clinical pharmacology studies were conducted in healthy male and female volunteers between the ages of 18 and 44 years. The studies were designed to show bioequivalence of Allegra-D 24 Hour to the reference products after a single dose and at steady state (Study M106455S/1001), and to assess the effect of high fat high calorie diet on the absorption of fexofenadine and pseudoephedrine from Allegra-D 24 Hour Tablets (Study

M106455S/1002). Reference products used were marketed fexofenadine HCl 180 immediate-release Tablets (Allegra) and pseudoephedrine HCl 240 mg extended-release (Sudafed 24 Hour) Tablets. The clinical pharmacology studies were reviewed in depth by the Office of Clinical Pharmacology and Biopharmaceutics (OCBP) Reviewer Dr. Al-Habet, and all submitted studies and additional safety data were reviewed by Medical Officer Dr. Lee. The OCBP team concluded that the pharmacokinetic profiles of Allegra-D 24 Hour are sufficiently similar to those of the reference listed drugs to support approval, and I concur with that conclusion.

The Cmax and AUC data from the two studies are shown in Table 1. For the single dose and multiple dose bioequivalence study the 90% CI were within the accepted 80% to 125% bioequivalence limit. The food effect study showed that food produced a large effect on fexofenadine, but not on pseudoephedrine (Table 1).

Table 1. Ratio between test and reference products (test/reference) for geometric LS mean values of PK parameters of fexofenadine and pseudoephedrine from various studies

		Fexofe	nadine	Pseudoep	hedrine
	PK parameter	Point estimate	90% CI	Point estimate	90% CI
Study 1001 (Sing	le dose) *		<del></del>	<u></u> .	
	Cmax	101.4	89.6-114.8	106.4	102.1-110.9
	AUC inf	102.4	94.5-111.1	93.6	89.8-97.5
Study 1001 (Stead	dy state) *		, ,,,		
	Cmax	108.0	96.7-120.7	103.4	97.9-109.1
	AUC inf	102.8	94.5-112.0	95.1	90.2-100.2
Study 1002 (Food	l effect) †				-
	Cmax	45.8	37.9-55.4	91.2	86.2-96.6
	AUC inf	58.4	51.0-66.9	90.7	87.8-93.8

<sup>\*</sup> Reference drugs: Marketed fexofenadine HCl 180 immediate-release Tablets (Allegra) and pseudoephedrine HCl 240 mg extended-release (Sudafed 24 Hour) Tablets

Literature report suggests that bioavailability of fexofenadine is affected by fruit juices such as grapefruit juice and apple juice. At the end-of-phase 2 meeting the Division asked Aventis to investigate the effect of fruit juices on fexofenadine. At the Division's request Aventis submitted results of these investigations during the review cycle. The submission included three studies (Studies 4141, 4143, and 4144) that assessed histamine induced skin wheal and flare response coupled with population pharmacokinetic analysis. These studies are reviewed in detail by the OCBP reviewer Dr. Al-Habet. These studies showed that grapefruit juice or orange juice reduced the exposure of fexofenadine by approximately 36%. The size of histamine induced skin wheal and flare was larger when fexofenadine was administered with either grapefruit juice or orange juice compared to water. The effect of food and fruit juices on the exposure of fexofenadine is substantial and is likely to affect the clinical efficacy of fexofenadine. The product label will reflect the findings of these studies and the label will state that the drug should be taken on empty stomach with water.

Single Allegra-D 24 Hour Tablet administered 30 minute after high-fat breakfast

Review of the safety data in the clinical pharmacology studies and two clinical studies that were submitted to NDA 20-872 did not reveal any safety signal. Review of the literature and US AERS database do not raise any safety concerns.

The clinical pharmacology studies were conducted in subjects down to the age of 18 years, but the applicant is seeking approval down to the age of 12 years. This is acceptable because the pharmacokinetic parameter is not expected to be different between children 12 through 18 years of age and subjects over 18 years of age. The safety is also not expected to be different in the 12 to 18 years age group.

# Pharmacology and Toxicology

The applicant did not conduct any new preclinical studies for this application because the active components of Allegra-D 24 Hour were previously studied by Aventis or others.

#### Data Quality, Integrity, and Financial Disclosure

There was one study center and one analytical site for the two clinical pharmacology studies. DSI audited the study center. No serious deficiencies were noted, DSI recommended acceptance of the studies. During review of these studies no issues with data quality and integrity were noted. All studies were conducted in accordance with accepted ethical standards. No financial disclosure issues were present.

#### **Pediatric Considerations**

The applicant is proposing an indication down to the age of 12 years and is not proposing to seek approval in patients below 12 years of age. This is acceptable because the fixed dose combination at the proposed dosage would not be suitable for children younger than 12 years of age.

#### **Product Name**

The trade name Allegra is approved and used by Aventis for the product line containing fexofenadine. The suffix "D 24 Hour" distinguishes this product as containing a decongestant and that the dosing frequency is 24 hours. DMETS and DDMAC find the proposed trade name acceptable. Aventis has submitted a supplemental application to the Agency to change the currently marketed Allegra D product to Allegra-D 12 Hour to distinguish the two products. This is reasonable. That application is currently under review.

#### Labeling

Aventis submitted a product label that generally conforms to the currently marketed Allegra and Allegra D product labels. The label has been reviewed by various disciplines. The Division and Aventis have agreed on a final labeling text. During comparative review of all labels containing fexofenadine the Division identified some differences and inconsistencies among the labels. For example, the drug interaction

information and food effect information was not consistent across the labels. The Division has communicated the inconsistencies to Aventis. The label of all products containing fexofenadine will be harmonized to make them consistent.

#### Action

The clinical pharmacology data and clinical safety data are sufficient to support approval of Allegra-D 24 Hour Tablets for use in patients ages 12 years and older for control of symptoms of seasonal allergic rhinitis. The CMC data also support approval of the product that was manufactured with the method proposed in the original application. Therefore, the action on this application will be APPROVAL. As stated above under the CMC section, Aventis will need to submit a prior approval supplement with supporting data to market the product manufactured with the process modification that Aventis mentioned to the Agency late in the review cycle.

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/s/

Badrul Chowdhury 10/19/04 01:03:11 PM MEDICAL OFFICER



# Food and Drug Administration Center for Drug Evaluation and Research Office of Drug Evaluation ODE II

# FACSIMILE TRANSMITTAL SHEET DATE: October 6, 2004 To: Kimberly S. Stranick, Ph.D. From: Christine Yu, R.Ph. Director, US Regulatory Affairs Regulatory Project Manager Company: Aventis Pharmaceuticals, Inc. Division of Pulmonary & Allergy Drug **Products** Fax number: 908-304-6317 Fax number: 301-827-1271 Phone number: 908-304-6580 Phone number: 301-827-1051 Subject: FDA proposed Package Inserts for NDA 21-704 Allegra-D 24 hour and NDA 20-786/S-017 Allegra-D 12 hour. Allegra products comparison table for reference Total no. of pages including cover: Comments: \*\* Provide response to this correspondence as soon as possible, but no later than 12:00 PM Friday, October 8, 2004. \*\* Document to be mailed: √ NO $\square$ YES

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# 25 Page(s) Withheld

\_\_\_\_\_ § 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

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/s/

Christine Yu 10/6/04 04:28:52 PM CSO



# Food and Drug Administration Center for Drug Evaluation and Research Office of Drug Evaluation ODE II

# FACSIMILE TRANSMITTAL SHEET DATE: October 15, 2004 To: Kimberly S. Stranick, Ph.D. From: Christine Yu, R.Ph Director, US Regulatory Affairs Regulatory Project Manager Company: Aventis Pharmaceuticals, Inc. Division of Pulmonary & Allergy Drug **Products** Fax number: 908-304-6317 Fax number: 301-827-1271 Phone number: 908-304-6580 Phone number: 301-827-1051 Subject: NDA 21-704 Allegra-D 24 hour CMC agreements Total no. of pages including cover: Comments: \*\* Please respond as soon as possible, no later than 12:00 pm Monday, October 18, 2004, \*\* Document to be mailed: √ NO □ YES

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# NDA 21-704 Facsimile October 15, 2004 CMC Agreements Page 2

We acknowledge your CMC amendments to NDA 21-704 dated August 26 and September 29, 2004. Your agreements to 1-4 below are acceptable. We must receive an agreement for the *new* commitment 5 below before this NDA may be approved. We request that you submit a formal response to the NDA agreeing to all five commitments.

1.	Agree to revise the drug product specifications according to the proposed agreements contained in your amendments dated August 26, 2004 and September 29, 2004.
	<ul> <li>a. Method</li></ul>
	c. The acceptance criterion for [ ] is NMT [ ] µg/tablet, and for [ ] is NMT [ ] µg/tablet. These acceptance criteria are implemented on an interim basis and subject to reexamination based on data from approximately —batches of post approval commercial production.
2.	Agree to revise the system suitability testing L 7 for the following analytical methods according to the proposed agreements contained in your amendment dated September 29, 2004:
	a. NMT L I for the system suitability testing L I for fexofenadine HCl and pseudoephedrine HCl.
	b. NMT L I for the system suitability L I method for L I
	c. NMT[ ] for the system suitability injections in the HPLC testing method for Dissolution.
3.	The following pertains to expiry dating and holding time:
	a. Agree (as per your amendment dated August 26, 2004) that the expiry-dating clock starts \(\Gamma\) at your Kansas City site.
•	b. A 24-month expiry dating is acceptable for the drug product packaged in 30ct, 100ct, L J HDPE bottle.
	c. A C J holding time is acceptable for bulk drug product packaged in C J and C J holding time is acceptable for bulk drug product packaged L J . As per your amendment dated August 26, 2004, agree to perform an additional hold study to confirm that the finished tablets stored in these bulk containers for the time periods indicated above, and then packaged in bottles (30 ct C J and blisters, remain within specification throughout the proposed shelf life of 24 month.
	d. A C I holding time is acceptable for C I pseudoephedrine — a  L I holding time is acceptable for C I pseudoephedrine — and a —  total holding time for C I combined is acceptable.

### NDA 21-704 Facsimile October 15, 2004 CMC Agreements Page 3

Agree to continue C	1 of the HDPE bottles at the C
stability time points for the I	NDA stability batches to further demonstrate the
effectiveness of the carbon c	anister throughout the remaining proposed shelf life of
the product, as stated in ame	ndment dated August 26, 2004.

5. Your stability database did not include  $\Gamma$  physician sample. However, based on the supporting stability testing data of  $\Gamma$  blister, an eighteen (18) month expiry dating is acceptable for the drug product packaged as  $\Gamma$  blister physician samples; provided you agree to conduct both long term and accelerated stability testing on this presentation for the first three (3) commercial batches, and include this presentation in your regular annual stability testing protocol. For future reference, all to-be-marketed packaging configurations (including physician samples) should be included in your NDA filings and annual stability protocols.

If you have questions about the contents of this facsimile, please contact Ms. Christine Yu at 301-827-1051.

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# Food and Drug Administration Center for Drug Evaluation and Research Office of Drug Evaluation ODE II

# FACSIMILE TRANSMITTAL SHEET

DATE:	September 13, 2004		Al		
To:	Kimberly S. Stranick, Ph.D Director, US Regulatory A		om: Christine Yu, R.Ph. Regulatory Project Manager		
Company	y: Aventis Pharmaceuticals, In	nc.	Division of Pulmonary & Allergy Drug Products		
Fax num	ber: 908-304-6317	Fa	x number: 301-827-1271		
Phone nu	mber: 908-304-6580	Ph	Phone number: 301-827-1051		
	NDA 21-704 Allegra-D 24h CMC and container labeling	comments			
Total no.	of pages including cover:	3			
Comment	ts:				
Document	t to be mailed:	□ YES	√ NO		

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# Facsimile correspondence September 13, 2004 Page 2

We refer to your NDA 21-704 and have the following comments and requests for information. Submission of timely responses would be appreciated.

1.	The following	comments	pertain to	o drug	product	specifications
----	---------------	----------	------------	--------	---------	----------------

a. Revise the acceptance criteria for L

I to be reflective of the data:

	Proposed	Release data	Suggested
ב	1	I	ا ت
t	<u> </u>		J

Taking into account the complexity of the process and limited manufacturing experience, the Agency suggested data-based acceptance (which is twofold higher than any observed value) should be implemented on an interim basis and subjected to reexamination based on sufficient data from post approval commercial productions (e.g., approximately —batches).

- 2. The following comments pertain to analytical method validations:
  - a. Tighten and submit revised [

]

b. Tighten and submit revised [

7

c. Tighten and submit revised [

٦

- 3. The following comments pertain to labeling:
  - a. For all container labels:
    - i. Relocate the "Rx only" statement to the principal display panel.
    - ii. Revise the "Dosage and Administration" statement to provide useful dosing information, e.g., "Take one tablet daily. See package insert for complete dosing information."

# Facsimile correspondence September 13, 2004 Page 3

b. Provide labeling information for all three drug product bulk containers L

- c. Provide labeling information for the [ 3 carton containing professional sample blister.
- d. Submit professional sample blister labels with the following revisions.
  - i. In the front, use the same description, font, and size for proprietary and USAN names.
  - ii. Indicate areas for lot number and expiration date.
  - iii. In the back, add proprietary name. Revise dosage statement as recommended in comment 3aii above.

If you have questions about the contents of this facsimile, please contact Christine Yu at 301-827-1051.

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/s/

Christine Yu 9/13/04 04:30:02 PM CSO

9/10/64

NDA 21-704 NDA Regulatory Filing Review Page 1

# NDA REGULATORY FILING REVIEW

(Including Memo of Filing Meeting)

NDA # Trade Name: Generic Name: Strengths:		21-704 (original) Allegra-D 24 hour Externation hydrochl 180 mg/240mg	ended Release tablets oride 180 mg/pseudoephe	drine HCL 240	mg ER	
Applicant:		Aventis Pharmaceutica	ls, Inc.			
Date of Application: Date of Receipt: Date clock started after UN: Date of Filing Meeting: Filing Date: Action Goal Date (optional):		19 December 2003 19 December 2003 N/A 3 February 2004 17 February 2004 5 October 2004 User Fee Goal Date: 19 October				
Indication(s) requested	:	Once daily relief of syr adults and children 12	nptoms associated with SA years of age and older.	AR with nasal co	ongestion in	
Type of Application:	(b)(1) S [If the	Supplement Original NDA was a (b)	Original (b)(2) N (b)(2) Suppleme (2), all supplements are (b) n be either a (b)(1) or a (b	nt )(2)s; if the Orig	ginal NDA	
NOTE: If the applicati summary.	on is a 5	05(b)(2) application, cor	mplete the 505(b)(2) section	on at the end of	this	
Therapeutic Classificat Resubmission after a w Chemical Classification Other (orphan, OTC, et	ithdrawa 1: (1,2,3		PResubmission after a refe	use to file? <u>N</u>	No	
User Fee Status:	Exemp	√ supplement fee t (orphan, government)	Waived (e.g., small busin		lth)	
Form 3397 (User Fee C User Fee ID # 4443		,		(YES)	NO	
Clinical data?	YES _	√ Referenced to NDA	s # <u>20-625, 20-872, 20-7</u>	86, 20-021 1	NO	
Is there any 5-year or 3	-year ex	clusivity on this active m	noiety in either a (b)(1) or	a (b)(2) applica	tion?	
If yes, explain: Aventis has pediatric u Alza has NDA 20-021	se mark vatent u	eting exclusivity that ex ntil March 14, 2006.	pires 11/12/2006.	YES	NO	
Does another drug have	orphan	drug exclusivity for the	same indication?	YES	(NO)	
If yes, is the dr [21 CFR 316.3			g according to the orphan	drug definition	of sameness	
( O. K. 510.5	(~)(*~)]:			YES	NO	

	the application affected by the Application Integrity Policy (AIP)? yes, explain.	YES	NO
	If yes, has OC/DMPQ been notified of the submission? YES	NO	
•	Does the submission contain an accurate comprehensive index?	YES	NO
•	Was form 356h included with an authorized signature?  If foreign applicant, both the applicant and the U.S. agent must sign.	YES	NO
•	Submission complete as required under 21 CFR 314.50? If no, explain:	YES	NO
•	If an electronic NDA, does it follow the Guidance? N/A  If an electronic NDA, all certifications must be in paper and require a signat Which parts of the application were submitted in electronic format?  Entire submission is electronic. Required certifications were submitted in paper. Additional comments:	ure. YES	NO
•	If in Common Technical Document format, does it follow the guidance? N/A	YES	NO
	Is it an electronic CTD?  If an electronic CTD, all certifications must be in paper and require a signat Which parts of the application were submitted in electronic format?  CMC section only is in CTD format. Entire NDA is electronic.  Additional comments: Hybrid submission.	YES ure.	NO
•	Patent information included with authorized signature?	YES	NO
•	Exclusivity requested? YES,	years esting exclusivity	is not
•	Correctly worded Debarment Certification included with authorized signature?  If foreign applicant, both the applicant and the U.S. Agent must sign the cert	YES tification.	NO
	NOTE: Debarment Certification must have correct wording, e.g.: "I, the undersi  Co. did not and will not use in any capacity the services of any per section 306 of the Federal Food, Drug and Cosmetic Act in connection with the s  ." Applicant may not use wording such as "To the best of my knowledge	son debarred une tudies listed in A	der
•	Financial Disclosure information included with authorized signature? (Forms 3454 and/or 3455 must be used and must be signed by the APPLICA	YES NT.)	NO
•	Field Copy Certification (that it is a true copy of the CMC technical section)?	YES	NO
Re	fer to 21 CFR 314.101(d) for Filing Requirements		
•	PDUFA and Action Goal dates correct in COMIS?  If not, have the document room staff correct them immediately. These are the date calculating inspection dates.	YES tes EES uses for	NO

•	Drug name/Applicant name correct in COMIS? If not, have the Document	t Room make the correct	ctions.
•	List referenced IND numbers: Yes.		
•	End-of-Phase 2 Meeting(s)?  If yes, distribute minutes before filing meeting.  Date(s)1/2 DFS	9/02 under IND 48,486	
•	Pre-NDA Meeting(s)?  If yes, distribute minutes before filing meeting.  Date(s) 8/2 DFS	7/03 under IND 66,289	
<u>Pr</u>	roject Management		
•	Package insert consulted to DDMAC? N/A	YES	NO
•	Trade name (plus PI and all labels and labeling) consulted to ODS/Div. of Technical Support?	Medication Errors and YES	NO
•	MedGuide and/or PPI (plus PI) consulted to ODS/Div. of Surveillance, Re	search and Communica	ition
	Support? N/A	YES	NO
•	If a drug with abuse potential, was an Abuse Liability Assessment, including submitted?	ng a proposal for sched	uling,
	N/A N/A	YES	NO
<u>If</u>	Rx-to-OTC Switch application:		
•	OTC label comprehension studies, all OTC labeling, and current approved	PI consulted to ODS/ I	Div. of
	!Surveillance, Research and Communication Support?	YES	NO
•	Has DOTCDP been notified of the OTC switch application?	YES	NO
<u>Cl</u>	<u>linical</u>		
•	If a controlled substance, has a consult been sent to the Controlled Substan	ce Staff? N/A	
<u>C</u>	<u>hemistry</u>		
•	Did applicant request categorical exclusion for environmental assessment?  For pseudoephedrine	VE8	NO
	If no, did applicant submit a complete environmental assessment?  For fexofenadine	$(_{YE})$	NO
	If EA submitted, consulted to Nancy Sager (HFD-357)?	N/A YES	NO
•	Not necessary per chemist based on assessment. Establishment Evaluation Request (EER) submitted to DMPQ?	(YES)	NO
•	If parenteral product, consulted to Microbiology Team (HFD-805)?	YES	NO

# If 505(b)(2) application, complete the following section:

•	Name of listed drug(s) and NDA/ANDA #: NDA 20-625, 20-872, 20-786, 20-021	
•	Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").  This application requests approval of a once daily dosage of fexofenadine and pseudocphedrine.	
	This application requests approval of a once daily dosage of jexofendatine and pseudocphearine.	
•	Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.)	
	YES (NO	<u>)</u>
•	Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9). Under review, not intentional	n
	YES (NO	(د
•	Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be	of
	refused for filing under 314.101(d)(9).  YES  NO	<u>)</u>
•	Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.	l.
	21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.	
	21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.	
	21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.	
	21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.	
	IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR $314.50(i)(1)(i)(A)(4)$ ], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR $314.52(b)$ ]. Subsequently, the applicant must subm documentation that the patent holder(s) received the notification ([21 CFR $314.52(e)$ ].	
	21 CFR 314.50(i)(1)(ii): No relevant patents.	
	21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indication that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.	
	21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)	r

Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

•	Did the	e applicant:			
	•	Identify which parts of the application rely on informathe applicant does not have a right of reference?	ation the applicant	t does not own o	r to which
				YES	NO
<ul> <li>Submit a statement as to whether the listed drug(s) identified has received a period of exclusivity?</li> </ul>		ed a period of m	narketing		
				YES	$\left( _{\mathrm{NO}}\right)$
	•	Submit a bioavailability/bioequivalence (BA/BE) studisted drug?	yES NO  study comparing the proposed product to the  N/A YES NO  adication and not for the indications approved ection for the approved indications and the CFR 314.54(a)(1)(iv).? See background  N/A YES NO  dicant submit the following information  and meets the definition of "new clinical YES NO  reports that are relevant to the conditions for YES NO  e studies essential to approval were conducted.  YES, IND # NO  of the clinical investigation(s) essential to rewhich those clinical studies were conducted?  N/A YES NO  seen notified of the existence of the (b)(2) application?		
			N/A	YES	NO
	•	Certify that it is seeking approval only for a new indiction for the listed drug if the listed drug has patent protection applicant is requesting only the new indication (21 CF information at the end of this review.	on for the approve	ed indications an	d the
		<b>,</b>	N/A	YES	NO
•		b)(2) applicant is requesting exclusivity, did the applicated by 21 CFR 314.50(j)(4):	ant submit the foll	owing informati	on
	•	Certification that each of the investigations included rinvestigation" as set forth at 314.108(a).	neets the definitio	n of "new clinica	al
				YES	NO
	•	A list of all published studies or publicly available rep which the applicant is seeking approval.	orts that are relev	ant to the condit	ions for
				YES	NO
	•	EITHER The number of the applicant's IND under which the st	udies essential to	approval were co	onducted.
		OR	YES, IND	#	NO
		A certification that it provided substantial support of tapproval if it was not the sponsor of the IND under with	he clinical investi hich those clinical	gation(s) essenti studies were co	al to nducted?
			N/A	YES	NO
•	Has the	e Director, Div. of Regulatory Policy II, HFD-007, beer	notified of the ex	xistence of the (b	)(2) application?
				YES	NO

#### **ATTACHMENT**

#### MEMO OF FILING MEETING

DATE:

February 3, 2004

#### BACKGROUND:

Aventis is seeking approval of a new fexofendine 180 mg/pseudoephedrine 240 mg extended release tablet to be taken once daily. At the EOP2 meeting on 1/29/02, the Division requested that Aventis submit a new NDA, versus submitting an efficacy supplement, because this extended release tablet  $\Gamma$ 

I (similar to Sudafed 24), unlike the Allegra-D tablet (approved for twice daily dosing). The Office of Regulatory Affairs (User Fee staff) has been notified of this administrative "split" from an efficacy supplement and that the NDA has been submitted. Aventis has paid the supplement fee.

On a separate issue, although NDA 20-786 for Allegra-D (fexofenadine 60 mg/pseudoephedrine 120mg) extended release tablet, approved 12/24/1997, was not processed as a 505b(2) application, NDA 21-704 will be processed as a 505b(2) application. Aventis has submitted an amendment to the NDA with patent 2 and 3 certifications to address this status but has noted that they do not agree with 505b(2) designation. [The initial NDA was submitted as a 505b(1)].

Kim Colangelo, of the Office of New Drugs, has been notified of this b(2) application.

#### ATTENDEES:

DPADP-

Christine Yu

Edwin Jao, Richard Lostritto

Joseph Sun

Sayed Al Habet, Tayo Fadiran

Charles Lee, Lydia Gilbert-McClain, Badrul Chowdhury

#### ASSIGNED REVIEWERS:

DSI:	Sent
Regulatory Project Manager:	Christine Yu
Microbiology, clinical (antimicrobial DP only):	
Microbiology, sterility:	
	Emmanuel Fadiran
Biopharmaceutical:	Shinja Kim
Environmental Assessment (if needed):	
	Richard Lostritto
Chemist:	Edwin Jao
Statistical Pharmacology:	
0. 1.1.45	Joseph Sun
Pharmacology:	Lawrence Sancilio
Statistical:	
Secondary Medical:	Lydia Gilbert-McClain
Medical:	Charles Lee
Discipline	

Version: 11/14/2003

Other Consults:		DMETS:	Sent	DDMAC: S	ent	
Per review If no, exp	vers, are all parts in E lain:	nglish or English	translatio	on?	YES	NO
CLINICAL		FILE <u>√</u>	ì	REFUSE TO FILE _		
• Clinic	cal site inspection need	ded:			YES	NO
• Advis	sory Committee Meeti	ng needed?	,	YES, date if known		NO
wheth	application is affected ner or not an exception sity or public health si	to the AIP shou				
				N/A	YES	NO
CLINICAL MICE	ROBIOLOGY	FILE	1	REFUSE TO FILE _		N/A)
STATISTICS		FILE	Ī	REFUSE TO FILE _		N/A
BIOPHARMACE	UTICS	FILE <u>√</u>	I	REFUSE TO FILE _		
• Bioph	narm. inspection neede	ed:			(YES)	NO
PHARMACOLO	ЗY	FILE <u>√</u>	I	REFUSE TO FILE _		
• GLP	inspection needed:				YES	(NO)
CHEMISTRY		FILE	I	REFUSE TO FILE _		
	lishment(s) ready for i biology	inspection?		N/A)	YES YES	NO NO
ELECTRONIC SI Any comments: in						
REGULATORY (	CONCLUSIONS/DEF	FICIENCIES:				
T	he application is unsu	itable for filing.	Explain w	/hy:		
	he application, on its for pears to be suitable for		e well org	ganized and indexed.	The application	on
	No filir	ng issues have be	en identif	ied.		
	_✓ Filing r	eview issues to b	e commu	nicated by Day 74.	List (optional):	

## **ACTION ITEMS:**

- 1. If RTF, notify everybody who already received a consult request of the RTF action. Cancel the EER.
- 2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
- 3. Document filing issues/no filing issues conveyed to applicant by Day 74.

Christine Yu, R.Ph. Regulatory Project Manager, HFD-570

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/s/

Christine Yu 9/10/04 12:23:36 PM CSO

Sandra Barnes 9/23/04 01:50:29 PM CSO



Food and Drug Administration Center for Drug Evaluation and Research Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET					
<b>DATE:</b> August 6, 2	2004				
•	S. Stranick, Ph.D. S Regulatory Affairs	From: Christine Yu, R.Ph. Regulatory Project Manager			
Company: Aventis Pharmaceuticals, Inc.		Division of Pulmonary & Allergy Dru			
Fax number: 908-304-6317		Fax number: 301-827-1271			
Phone number: 908-3	04-6580	Phone number: 301-827-1051			
Subject: NDA 21-704 Notification	Allegra-D 24 Hour of DMF Deficiency	<u> </u>			
Total no. of pages incl	uding cover: 2	From: Christine Yu, R.Ph.  Regulatory Project Manager  Division of Pulmonary & Allergy Drug  Products  Fax number: 301-827-1271			
Comments:					
Document to be mailed	: □ YES	√ NO			

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# NDA 21-704 Facsimile correspondence August 6, 2004 Page 2

We refer to your NDA 21-704 for Allegra-D 24 Hour Extended-Release tablets.

The following comment pertains to  $\mathcal{L}$  Jearbon pouch in DMF  $\mathcal{L}$ 

J

The DMF is inadequate to support your NDA. A letter will be sent to the DMF holder under a separate cover. Contact the DMF holder to discuss any deficiencies or clarifications.

If you have questions about the contents of this facsimile, please contact Christine Yu at 301-827-1051.

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/s/

Christine Yu 8/6/04 12:43:21 PM CSO



Food and Drug Administration Center for Drug Evaluation and Research Office of Drug Evaluation ODE II

<del>- ***</del>	FACSIMILE TRANSMITTAL SHEET					
DATE:	July 15, 2004					
To:	Kimberly S. Stranick, Ph.D Director, US Regulatory At		From: Christine Yu, R.Ph. Regulatory Management Officer			
Compan	y: Aventis Pharmaceuticals, Ir	ic.				
Fax num	ber: 908-304-6317		Fax number: 301-827-1271			
Phone nu	ımber: 908-304-6580	. ,	Phone number: 301-827-1051			
Subject:	NDA 21-704 CMC Information	mberly S. Stranick, Ph.D. rector, US Regulatory Affairs ventis Pharmaceuticals, Inc  908-304-6317  Fax number: 301-827-1271  r: 908-304-6580  Phone number: 301-827-1051  A 21-704 CMC Information Request  nges including cover: 2				
Total no.	of pages including cover.	2				
Commen	ts:					
Document to be mailed: ☐ YES    √ NO						

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# NDA 21-704 CMC Information Request Page 2

Please refer to NDA 21-704 dated December 19, 2003, for Allegra-D 24 hour Extended –Release Tablets. We have the following request for information (Your efforts for a prompt response will be appreciated.)

	or appropriate att,					
1.	The following comm	ents pertain to the	pseudoephedrine HO	CLC J		
	a. Provide an explaid label claim L	nation as to why al	ll three NDA stability	batches are below		
	b. Provide an explai	nation C	-			
	c. Provide information about the container closure system for bulk pseudoephedrine HCl [ ] to Aventis, MO.					
	<ul><li>d. Provide acceptan</li><li>C</li><li>testing.</li></ul>	ce criteria used by		pseudoephedrine HCl of HPLC, should be used for		
	e. Establish holding appropriate stabil the investigation.	time for pseudoepity testing data. D	ohedrine HCl C rug product expiry n	J'ased on nay depend on the outcome of		
2.	The following comments pertain to the fexofenadine C 7					
	Until the method is recommend that you			d drug product, we		
3.	The following comm	ents pertain to drug	g product specification	ons:		
	a. Revise the accept	ance criteria . C	フ; to be	reflective of the data:		
		Proposed	Release data	Suggested		
ב				L.		
Ĺ				J		
			<del></del>	1		

# NDA 21-704 CMC Information Request Page 3

b. Revise the acceptance criteria  $\mathcal{L}$  be reflective of the data:

ightharpoonup of J of Fexofenadine HCl to

	Release data (all batches)	proposed criterion	e.g. revised criterion	stability data (all batches, all conditions)	Proposed criteria	Suggested e.g. criteria
Total	C			1		כ

c.	Provide an explanation of [
	J demonstrated in Figure 1 to 4 and figure 23-54.

- 4. The following comments pertain to stability and expiry dating of the drug product:
  - a. The moisture content in all trade packages and bulk containers display an upward trend (although still within specification) during stability testing, and more so for blister and bulk containers. Provide evidence that the drug product stored in the proposed bulk containers to the proposed maximum storage time can still be stored in the proposed trade packages to the balance of the proposed expiry dating. Otherwise, the expiry dating can only be determined based on the data and appropriate extrapolation under the worst case scenario (e.g., the least protective package).
  - b. You have not provided data demonstrating that the carbon canisters have adequate activity and L J in the HDPE bottles and that the moisture does not C stability testing. Therefore, monitor and report the L J HDPE bottles with and without the carbon canisters to prove efficacy of its intended use for the entire shelf life of the drug product.
- 5. The following comments pertain to the container/closure system:

Provide adequate information [	
	I for two bulk storage
containers: [	J For each referenced DMF,
provide LOAs with the location of most curr	rent and relevant information, i.e., section,
page, and date of letter.	,

6. The following comment pertains to labeling:

Provide labeling information for bulk packaging \( \) J blisters.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Christine Yu 7/15/04 05:08:00 PM CSO

# **CONSULTATION RESPONSE**

**Division of Medication Errors and Technical Support** Office of Drug Safety

(DMETS: HFD-420)

DATE RECEIVED:

**DESIRED COMPLETION DATE: May 7, 2004** 

February 24, 2004

PDUFA DATE: October 19, 2004

**ODS CONSULT#:** 

NDA SPONSOR:

Aventis Pharmaceuticals, Inc.

04-0074

TO:

Badrul Chowdhury, M.D.

Director, Division of Pulmonary and Allergy Drug Products

HFD-570

**THROUGH:** Christine Yu, R.Ph.

Project Manager, Division of Pulmonary and Allergy Drug Products

HFD-570

PRODUCT NAME:

Allegra-D 24 Hour™

(Fexofenadine HCl and Pseudoephedrine HCl Extended-release Tablets)

180 mg/240 mg

NDA#: 21-704

SAFETY EVALUATOR: Scott Dallas, R.Ph.

**RECOMMENDATIONS:** 

1. DMETS has no objections to the use of the proprietary name, "Allegra-D 24 Hour™" provided the sponsor adds an appropriate modifier (e.g., 12 Hour) to the proprietary name, Allegra-D (NDA 20-786) prior to the launch of Allegra-D 24 Hour™ to further differentiate these products.

- 2. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review to minimize potential errors with the use of this product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.
- 3. DDMAC finds the proprietary name, "Allegra-D 24 Hour™" acceptable from a promotional perspective.

Carol Holquist, R.Ph.

Division of Medication Errors and Technical Support

Office of Drug Safety

Phone: (301) 827-3242 Fax (301) 443-9664

# Division of Medication Errors and Technical Support Office of Drug Safety HFD-420; Parklawn Building Room 6-34 Center for Drug Evaluation and Research

# PROPRIETARY NAME REVIEW

DATE OF REVIEW:

April 15, 2004

NDA NUMBER:

21-704

NAME OF PRODUCT:

Allegra-D 24 Hour™

(Fexofenadine HCI and Pseudoephedrine HCI Extended-release

Tablets)

180 mg/240 mg

**NDA SPONSOR:** 

Aventis Pharmaceuticals, Inc.

## I. INTRODUCTION:

This consult was written in response to a request from the Division of Pulmonary and Allergy Drug Products for an assessment of the proposed proprietary name, Allegra-D 24 Hour™. Container labels and package insert labeling were provided for review and comment.

# **PRODUCT INFORMATION**

Allegra-D 24 Hour™ is a combination product of fexofenadine hydrochloride and pseudoephedrine hydrochloride. Fexofenadine hydrochloride is an antihistamine with selective peripheral H₁-receptor antagonist activity and pseudoephedrine hydrochloride is a sympathomimetic amine. Each Allegra-D 24 Hour™ tablet contains 180 mg of fexofenadine hydrochloride and 240 mg pseudoephedrine hydrochloride. The combination is indicated for the relief of symptoms associated with seasonal allergic rhinitis in adults and children 12 years of age and older. The recommended dose of Allegra-D 24 Hour™ is one tablet once daily administered before a meal.

# II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts<sup>1, 2</sup> as well as several FDA databases<sup>3</sup> for existing drug names which sound-alike or look-alike to "Allegra-D 24 Hour™" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's trademark

<sup>&</sup>lt;sup>1</sup> MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

<sup>&</sup>lt;sup>2</sup> Facts and Comparisons, 2004, Facts and Comparisons, St. Louis, MO.

<sup>&</sup>lt;sup>3</sup> The Drug Product Reference File [DPR], the DMETS database of proprietary name consultation requests, New Drug Approvals 98-04, and the electronic online version of the FDA Orange Book.

electronic search system (TESS) was conducted<sup>4</sup>. The Saegis<sup>5</sup> Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted prescription analysis studies, involving health care practitioners within FDA. These exercises were conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the names.

# A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name "Allegra-D 24 Hour". Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

- 1. DDMAC finds the proprietary name, "Allegra-D 24 Hour™", acceptable from a promotional perspective.
- 2. The Expert Panel did not identify any proprietary names that were thought to have the potential for sound or look-alike confusion with "Allegra-D 24 Hour™", except the proprietary names Allegra and Allegra-D. These products are listed in Table 1 (see below), along with the dosage form available and usual dosage.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Established name, Dosage form(s), and Strength(s)	Usual adult dose*	Other**
Allegra-D-24 Hour <sup>TM</sup>	Pseudoephedrine HCl	Take 1 tablet daily.	
	Extended-Release Tablets, 180 mg/240 mg		
Allegra	Fexofenadine HCl, Tablets, 30 mg, 60 mg, and 180 mg Capsules, 60 mg	Adults and children 12 years of age and older: Take 60 mg twice daily or 180 mg once daily.	SA/LA
Allegra-D	Fexofenadine HCl and Pseudoephedrine HCl Extended- Release Tablets, 60 mg/120 mg	Take 1 tablet twice daily.	SA/LA
• •	l, not all-inclusive. e), S/A (sound-alike)		

LIA (100K-allke), SIA (sound-allke)

<sup>4</sup> WWW location http://www.uspto.gov/main/trademarks.htm

<sup>&</sup>lt;sup>5</sup> Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

# B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. The Expert Panel (EPD) discussed all names identified in POCA that were considered to have significant phonetic or orthographic similarities to Allegra-D 24 Hour.

# C. ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE SEARCH

DMETS searched the FDA Adverse Event Reporting System (AERS) database for any post-marketing safety reports of medication errors involving "Allegra", and "Allegra-D". The MedDRA Preferred Term (PT) "Medication Error", the tradenames, and verbatim for "Alleg%" and "Fexofe%" were used to perform the searches. The search revealed that there was some potential confusion due to the look-alike labeling of the Allegra product line. There was a report of an actual error, in which Allegra tablets, 60 mg, were dispensed instead of Allegra capsules, 60 mg. Additionally, the search revealed that there was confusion and an actual medication error due to scripted look-alike similarities of the proprietary names Allegra-D and Allerx-D. The search also revealed two actual errors due to the potential for the proprietary name Allegra to sound and or look similar to the proprietary name Viagra. There was one report of potential confusion due to the look-alike similarities between Allegra capsules and Actigall capsules, and because both products have the potential to be stored in close proximity to each other. DMETS will continue to monitor post-marketing error reports involving Allegra, Allegra-D and these other products.

# D. PRESCRIPTION ANALYSIS STUDIES

# 1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of "Allegra-D 24 Hour™" with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 124 health care professionals (pharmacists, physicians, and nurses) for the proposed proprietary name. These exercises were conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for "Allegra-D 24 Hour™". These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via email. In addition, outpatient orders were recorded on voice mail and included an order for "Allegra-D 24 Hour™". The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
Outpatient:	Outpatient:
Alleya Dog. 29h.	Allegra-D 24 Hour Take one po qd Number 30
Inpatient:  Stran 65 00+5	

#### 2. Results:

One participant in the written inpatient prescription study interpreted the proposed name as Allegra 24 hr. A total of twelve participants in the inpatient and outpatient prescription studies interpreted the proposed name as Allegra D and did not include the modifier "24 hour". See Attachment A for the complete listing of interpretations from the verbal and written prescription studies.

# E. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proposed proprietary name "Allegra-D 24 Hour™", the primary concerns related to look-alike and sound-alike confusion with Allegra and Allegra-D. Additionally, no names of concern were identified using POCA. DMETS also conducted prescription studies to simulate the prescription ordering process. In this case, there was confirmation that the proposed name, Allegra-D 24 Hour™, could be confused with Allegra and Allegra-D. Although there are limitations to the predictive value of these studies, primarily due to sample size, we have acquired safety concerns due to the positive interpretation with this drug product. A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population.

#### 1. Look-alike and Sound-alike Concerns

DMETS acknowledges that the current accepted practice is to add an appropriate suffix to an existing proprietary name in order to create a unique proprietary name for a new modified release dosage formulation of a medication. Although the addition of a modifier has been an accepted practice to identify a new modified dosage formulation, it has not been a perfect system. In this case the sponsor has proposed to add the modifier "24 Hour" to the proprietary name "Allegra-D". If approved this would create a product line with three proprietary names, Allegra, Allegra-D, and Allegra-D 24 Hour. It would also create a product line in which each subsequent proprietary name is longer than the previously approved proprietary name. Therefore, DMETS is concerned that increasing the length of the proprietary name would increase the risk that the modifier is omitted from the proprietary name. If the modifier, 24 Hour, is omitted, then the product

will be confused with the product Allegra-D. Medication prescribing practices indicate that healthcare professionals will abbreviate (e.g., HCTZ for hydrochlorothiazide) and or even omit parts of the proprietary name (e.g., Z-Pak for Zithromax Z-Pak), if the healthcare professional believes the identity of the product has been safely communicated. Therefore, if healthcare professionals do not fully understand the importance of the modifier "24-Hour", then healthcare professionals may not include the modifier on an order. As previously stated if the modifier, 24 Hour, is not communicated, then the intended product, Allegra-D 24 Hour™ would be communicated as Allegra-D. Post-marketing error reports and independent research has indicated that the omission of modifiers continues to cause medication errors. Timothy S. Lesar, Pharm.D. conducted research at a 631-bed teaching hospital in order to evaluate prescribing errors involving medication dosage forms. 6 Detailed analysis of 402 medication errors over a 16 month period (Sept. 1999 to Dec. 2000) demonstrated that the most common error was due to the failure to specify a controlled release dosage formulation (280 cases or 69.7%). Studies such as this one, support DMETS concern that healthcare professionals may fail to include the modifier, "24 Hour", on a prescription. Errors due to the omission of the modifier, 24 Hour, would be very difficult to detect since the order would correctly identify the product, Allegra-D, and the directions for use could be written as "Take one tablet daily" for both products. Therefore, it is very important that healthcare professionals and consumers are educated about differences between the two different antihistamine/decongestant combination products, and the importance of including the modifier "24 Hour" to identify the "Allegra-D 24 Hour" product.

In order to further differentiate the products, Allegra-D and Allegra-D 24 Hour, DMETS believes an appropriate modifier such as "12 Hour" should be associated with Allegra-D (NDA 20-786). This would create proprietary names, in which the modifiers would identify the normal dosing schedule for that product. The addition of a modifier to Allegra-D, would also eliminate the use of the proprietary name Allegra-D, since Allegra-D would no longer identify a specific product. The significance of this additional modifier would be to prevent errors in which the omission of the modifier, 24 Hour, on an order could be interpreted as Allegra-D. If a modifier were required to identify both medications, then any modifier omission would alert the listener or reader that the order was incomplete. Therefore, healthcare professionals and consumers must be educated to understand that the modifiers, "12 Hour" and "24 Hour", are significant and necessary to correctly identify a specific product.

The modifiers "12 Hour" and "24 Hour" are already being used to differentiate two loratedine/pseudoephedrine sulfate medications for the product line extension of Claritin. DMETS has not received any post-marketing error reports involving confusion between the products Claritin-D 12 Hour and Claritin-D 24 Hour. Examples of the carton labels for Claritin-D 12 Hour and Claritin-D 24 Hour are included for review (see page 7).

<sup>&</sup>lt;sup>6</sup> Lesar, Timothy S. Prescribing Errors involving Medication Dosage Forms. J Gen. Intern. Med.2002;17:579-87.





Therefore, DMETS recommends that proactive measures be taken before the launch of the second fexofenadine HCl/pseudoephedrine HCl dosage formulation is approved for distribution in the marketplace, to add the modifier "12 Hour" to the proprietary name of Allegra-D. The use of the modifiers "12 Hour" and "24 Hour" should help to further differentiate Allegra-D from Allegra-D 24 Hour.

# 2. Introduction of a New Dosage Formulation into the Marketplace

Post-marketing medication error reports indicate that healthcare professionals may be uninformed that a new dosage formulation is available and therefore continue to make medication errors months after the distribution date (not the approval date) of a new dosage formulation. By examining medication error reports submitted to the FDA, it becomes evident that a long period of time may be required for healthcare professionals to learn that a new dosage formulation has been marketed. One such example involved the extension of the Metadate product line. Metadate ER 20 mg, a methylphenidate product with a twice a day dosing frequency was approved on June 1, 1988. Then the product line was extended with the approval of Metadate CD 20 mg on April 3, 2001, a methylphenidate product with a once daily dosing frequency. The distribution of this second product, Metadate CD began on November 15, 2001. One medication error report submitted to the FDA involved a pharmacist who dispensed Metadate ER to 3 patients on 6 occasions, [January 02, February 02 (2x), March 02, and April 02 (2x)], instead of Metadate CD, because the pharmacist was unaware of the new product. The report also states that the pharmacist discovered this error after reading a newsletter that contained excerpts on errors involving these two products. Therefore, this pharmacist did not discover a new dosage formulation was available until after the product had been in distribution for 6 months, or one year after the approval date of the product. Thus DMETS also recommends that the sponsor conduct a comprehensive education campaign prior to and during the introduction of this new dosage formulation into the marketplace (see Section III below).

If the Division agrees with DMETS that an appropriate modifier, (e.g., 12 Hour) should be added to the proprietary name, Allegra-D (NDA 20-786) to further differentiate Allegra-D and Allegra-D 24 Hour, then educating healthcare professionals and consumers becomes very important. If the name Allegra-D is changed to Allegra-D 12 Hour, then there will be 3 proprietary names and labeling in the marketplace for two

different products. Pharmacists could conceivably have containers for Allegra-D. Allegra-D 12 Hour, and Allegra-D 24 Hour on their pharmacy shelf at the same time, and at the same time receive prescriptions written by physicians as "Allegra-D, one tablet daily". Healthcare professionals and consumers must be educated that Allegra-D 12 Hour will be the new name for Allegra-D, and that there has been no change in this dosage formulation. Healthcare professionals and consumers must be educated that a new dosage formulation containing more fexofenadine HCl and pseudoephedrine HCl will be marketed under the proprietary name, Allegra-D 24 Hour. Also that the modifiers, 12 Hour and 24 Hour, identify the normal dosing frequency for the product. Healthcare professionals must be educated that orders for Allegra-D do not clearly identify a specific product and that all orders for Allegra-D should be corrected to include the modifier 12 Hour or 24 Hour. During this transition period, it is extremely important for pharmacists and nurses to be educated that they must be vigilant for any orders communicated as "Allegra-D, Take one tablet daily". If a healthcare professional receives an order for Allegra-D, then the healthcare professional must be educated and instructed to contact the prescribing physician to clarify and correct the order. These are some of the issues that should be addressed in the comprehensive education campaign prior to and during the introduction of the new dosage formulation and proprietary names into the marketplace.

# III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In review of the container label, and package insert labeling of Allegra-D 24 Hour™, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified several areas of possible improvement, which might minimize potential user error.

# 1. CONTAINER LABELS

a. Increase the prominence of the proprietary name, Allegra-D 24 Hour™.

b. (

- c. DMETS recommends that the "Rx only" statement be relocated to the principal display panel.
- d. DMETS recommends that the "Dosage and Administration" statement provide useful dosing information, since a specific and usual dose is recommended for this product in the package insert labeling. (e.g., Usual dose: Take one tablet daily. See package insert for complete dosing information.)

# 2. CARTON LABELING

No carton labeling was available at this time for comment.

# 3. PACKAGE INSERT LABELING

DMETS has no comments at this time.

#### 4. EDUCATION

Post-marketing experience indicates that medication errors occur when healthcare professionals are unaware that a new modified dosage formulation of a medication has been introduced into the marketplace. Therefore, DMETS recommends the sponsor conduct an education campaign prior to and during the introduction of this product into the marketplace. Also if an appropriate modifier (e.g., 12 Hour) is added to the proprietary name of Allegra-D, then the education campaign should address the transitional period when there would be three proprietary names (e.g., Allegra-D, Allegra-D 12 Hour, and Allegra-D 24 Hour) for two different drug products. The education campaign should alert all healthcare professionals concerning the need to include a modifier on all orders, the differences between the products within the Allegra product line, and how to safety prescribe the products in order to prevent medication errors.

# IV. RECOMMENDATIONS:

- DMETS has no objections to the use of the proprietary name "Allegra-D 24 Hour™"
  provided the sponsor adds an appropriate modifier (e.g., 12 Hour) to the proprietary name,
  Allegra-D (NDA 20-786) prior to the launch of Allegra-D 24 Hour™ to further differentiate
  these products.
- DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.
- 3. DDMAC finds the proprietary name, "Allegra-D 24 Hour" acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam at 301-827-3242.

/\$/

Scott Dallas, R.Ph. Safety Evaluator Office of Drug Safety (DMETS)

/\$/

Concur:

Denise Toyer, Pharm.D.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

Attachment A:

Prescription Study Results for the proposed name "Allegra-D 24 Hour"

Inpatient Written	Outpatient Written	Voicemail
Allegra 24 hr	Allegra D	Alegra d 24 h
Allegra D	Allegra D	Allegra D 24 Hour
Allegra D	Allegra D	Allegra D 24 hour
Allegra D	Allegra D	Allegra D 24 hour
Allegra D	Allegra D	Allegra D 24 hour
Allegra D	Allegra D	Allegra D 24 hour
Allegra D	Allegra D 24 h	Allegra D 24 hr
Allegra D - 24 Hour	Allegra D 24 Hour	Allegra D 24 hr
Allegra D 24	Allegra D 24 hour	Allegra D 24 hr
Allegra D 24 hour	Allegra D 24 Hour	Allegra D 24-Hour
Allegra D 24 hour	Allegra D 24 hour	Allegra D 24-hour
Allegra D 24 hour	Allegra D 24 hr	Allegra D24 hours
Allegra D 24 hour	Allegra D 24H	Allegra-D 24 hour
Allegra D 24 hour	Allegra D 24h	Allegra-D 24 hour
Allegra D 24 hour	Allegra D 24h	Allegra-d 24 hour
Allegra D 24 hour	Allegra D 24h	Allegra-D 24 Hour
Allegra D 24 Hour	Allegra D 24H	Allegra-D 24 hour
Allegra D 24 hours	Allegra D 24 h	Allegra-D 24 hr
Allegra D 24 hr	Allegra-D 24 hour	Allegra D 24hour
Allegra D 24-hour	Allergra D 24h	
Allegra ID		
Allegra-D 24 Hour		
Allegra-D 24 hour		
Allergan D 24 hour		

# This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Scott Dallas 7/1/04 01:08:04 PM DRUG SAFETY OFFICE REVIEWER

Denise Toyer 7/1/04 02:46:20 PM DRUG SAFETY OFFICE REVIEWER

Carol Holquist
7/1/04 02:58:12 PM
DRUG SAFETY OFFICE REVIEWER

SEPOBC3/3/04 DEPARTMENT OF HEALTH AND HUMAN SERVICES **PUBLIC HEALTH SERVICE** REQUEST FOR CONSULTATION FOOD AND DRUG ADMINISTRATION TO (Division/Office): FROM: Division of Drug Marketing, Advertising and Communications, HFD-42 Christine Yu. R.Ph. PKLN Room 17b-17 Division of Pulmonary & Allergy Drug Products, HFD-570 IND NO. NDA NO. TYPE OF DOCUMENT DATE OF DOCUMENT 4 March 2004 21-704 Original NDA 19 December 2004 NAME OF DRUG PRIORITY CONSIDERATION CLASSIFICATION OF DRUG **DESIRED COMPLETION DATE** Allegra-D 24 hour ER tablet Standard 3 30 June 2004 (fexofenadine 180 mg/ pseudoephedrine 240mg) NAME OF FIRM: Aventis Pharmaceuticals, Inc. **REASON FOR REQUEST** I. GENERAL □ NEW PROTOCOL ☐ PRE-NDA MEETING ☐ RESPONSE TO DEFICIENCY LETTER PROGRESS REPORT ☐ END OF PHASE II MEETING ☐ FINAL PRINTED LABELING □ NEW CORRESPONDENCE □ RESUBMISSION □ LABELING REVISION □ DRUG ADVERTISING ☐ SAFETY/EFFICACY ORIGINAL NEW CORRESPONDENCE □ ADVERSE REACTION REPORT ☐ PAPER NDA ☐ FORMULATIVE REVIEW ■ MANUFACTURING CHANGE/ADDITION □ CONTROL SUPPLEMENT ☐ OTHER (SPECIFY BELOW): □ MEETING PLANNED BY II. BIOMETRICS STATISTICAL EVALUATION BRANCH STATISTICAL APPLICATION BRANCH ☐ TYPE A OR B NDA REVIEW ☐ CHEMISTRY REVIEW ☐ END OF PHASE II MEETING □ PHARMACOLOGY CONTROLLED STUDIES □ BIOPHARMACEUTICS □ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW): THER (SPECIFY BELOW): III. BIOPHARMACEUTICS DISSOLUTION ☐ DEFICIENCY LETTER RESPONSE ■ BIOAVAILABILTY STUDIES □ PROTOCOL-BIOPHARMACEUTICS PHASE IV STUDIES □ IN-VIVO WAIVER REQUEST IV. DRUG EXPERIENCE ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY  $\hfill \square$  DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES ☐ SUMMARY OF ADVERSE EXPERIENCE ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below) ☐ POISON RISK ANALYSIS ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP V. SCIENTIFIC INVESTIGATIONS ☐ CLINICAL □ PRECLINICAL COMMENTS/SPECIAL INSTRUCTIONS: Please perform DDMAC review of original NDA 21-704. Entire application is electronically available in EDR. Please contact me if you have any questions at 827-1051. SIGNATURE OF REQUESTER METHOD OF DELIVERY (Check one)

SIGNATURE OF RECEIVER

□ MAIL

SIGNATURE OF DELIVERER

DY HAND



#### **DEPARTMENT OF HEALTH & HUMAN SERVICES**

**Public Health Service** 

Food and Drug Administration Rockville, MD 20857

FILING COMMUNICATION

3/2/04

NDA 21-704

Aventis Pharmaceuticals, Inc. 200 Crossing Blvd. P.O. Box 6890 Bridgewater, NJ 08807-0890

Attention:

Kimberly S. Stranick, Ph.D. Director, Regulatory Liaison U.S. Regulatory Affairs

Dear Dr. Stranick:

Please refer to your December 19, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Allegra-D (fexofenadine HCl 180 mg and pseudoephedrine HCl 240 mg) 24 hour Extended Release tablet.

We also refer to your submission dated February 17, 2004.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on February 17, 2004, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issue:

At the End-of-Phase II meeting held January 29, 2002, under IND 48,486, we had recommended that you study the effects of grapefruit and apple juices on fexofenadine bioavailability. Provide information from or about the status of this/these study(ies).

We are providing the above comments to give you preliminary notice of <u>potential</u> review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Our facsimile correspondence requesting additional Chemistry, Manufacturing and Controls (CMC) information to facilitate our review was sent February 13, 2004.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

NDA 21-704 Page 2

If you have any questions, call Ms. Christine Yu, R.Ph., Regulatory Project Manager, at (301) 827-1051.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D. Director Division of Pulmonary and Allergy Drug Products Office of Drug Evaluation II Center for Drug Evaluation and Research This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Badrul Chowdhury 3/2/04 03:57:01 PM

40/12/2 3 and Oce DEPARTMENT OF HEALTH AND HUMAN SERVICES **PUBLIC HEALTH SERVICE** REQUEST FOR CONSULTATION **FOOD AND ORUG ADMINISTRATION** TO (Division/Office): FROM: Pirector, Division of Medication Errors and Christine Yu, R.Ph. echnical Support (DMETS), HFD-420 Regulatory Project Manager, HFD-570 KLN Rm. 6-34 IND NO. NDA NO. TYPE OF DOCUMENT DATE OF DOCUMENT 24 February 2004 21-704 Original NDA 19 December 2004 NAME OF DRUG PRIORITY CONSIDERATION CLASSIFICATION OF DRUG DESIRED COMPLETION DATE Allegra-D 24 hour ER tablet Standard Standard 30 June 2004 (fexofenadine HCI 180 mg/ pseudoephedrine HCI 240 ma) NAME OF FIRM: Aventis Pharmaceuticals, Inc. **REASON FOR REQUEST** I. GENERAL □ NEW PROTOCOL PRE-NDA MEETING THE RESPONSE TO DEFICIENCY LETTER □ PROGRESS REPORT ☐ END OF PHASE II MEETING ☐ FINAL PRINTED LABELING □ NEW CORRESPONDENCE □ RESUBMISSION ☐ LABELING REVISION ☐ DRUG ADVERTISING □ SAFETY/EFFICACY ☐ ORIGINAL NEW CORRESPONDENCE □ ADVERSE REACTION REPORT PAPER NDA ☐ FORMULATIVE REVIEW ■ MANUFACTURING CHANGE/ADDITION □ CONTROL SUPPLEMENT ☑ OTHER (SPECIFY BELOW): MEETING PLANNED BY Trade name review #. BIOMETRICS TICAL EVALUATION BRANCH STATISTICAL APPLICATION BRANCH E A OR B NDA REVIEW \_ND OF PHASE II MEETING ☐ CHEMISTRY REVIEW □ PHARMACOLOGY □ CONTROLLED STUDIES ☐ PROTOCOL REVIEW □ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW): □ OTHER (SPECIFY BELOW): III. BIOPHARMACEUTICS □ DISSOLUTION ☐ DEFICIENCY LETTER RESPONSE ☐ BIOAVAILABILTY STUDIES ☐ PROTOCOL-BIOPHARMACEUTICS □ PHASE IV STUDIES ☐ IN-VIVO WAIVER REQUEST IV. DRUG EXPERIENCE ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY D DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES ☐ SUMMARY OF ADVERSE EXPERIENCE CASE REPORTS OF SPECIFIC REACTIONS (List below) POISON RISK ANALYSIS COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP V. SCIENTIFIC INVESTIGATIONS ☐ CLINICAL D PRECLINICAL COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS: Entire submission available in EDR. PDUFA DATE: 10/19/04 ATTACHMENTS: Draft Package Insert, Container and Carton Labels NDA 21-704 570/RPM/C Yu JRE OF REQUESTER METHOD OF DELIVERY (Check one) ☐ MAIL DIVAH X SIGNATURE OF RECEIVER ... SIGNATURE OF DELIVERER



February 17, 2004

Badrul Chowdhury, M.D., Ph.D., Director Food and Drug Administration Center for Drug Evaluation and Research Division of Pulmonary and Allergy Drug Products (HFD-570) Central Document Room 12229 Wilkins Avenue Rockville, Maryland 20857

# NDA AMENDMENT NDA 21-704 ALLEGRA-D 24 HOUR™ Extended Release Tablets

Dear Dr. Chowdhury:

Reference is made to NDA 21-704 ALLEGRA-D 24 HOUR<sup>TM</sup> (fexofenadine hydrochloride 180mg and pseudoephedrine hydrochloride 240mg) Extended-Release Tablets submitted to the Agency on December 19, 2003 seeking approval for ALLEGRA-D 24 HOUR to be administered once daily for the relief of symptoms associated with seasonal allergic rhinitis with nasal congestion in adults and children 12 years and older. Reference is also made to a telephone conversation between the undersigned and Ms. Christine Yu, Regulatory Management Officer, Division of Pulmonary & Allergy Drug Products, which took place on February 6, 2004.

In that conversation, Ms. Yu advised that upon review of this application, the Agency had determined that this NDA would be considered under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. Additionally, Ms. Yu requested that Aventis provide by February 17, 2004 appropriate patent certification(s) pursuant to 21 CFR §314.50(i)(1)(i)(A).

Aventis does not agree with the Agency's designation of this NDA as a type 505(b)(2) application, and respectfully reserves the right to revisit this issue or challenge this determination in future. However, in order to maintain the user fee goal date for the Agency's review of this application, Aventis submits the enclosed certification documentation for Item 14 of NDA 21-704. Aventis respectfully reserves the right to submit revised certifications for this application.

Aventis Pharmaceuticals Inc.
NDA 21-704 (ALLEGRA-D 24 HOUR™ Extended Release Tablet) AMENDMENT
February 17, 2004
Page 2

Aventis considers the information included in this submission to be confidential and proprietary, and requests that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Aventis Pharmaceuticals according to CFR §314.430.

On behalf of Aventis Pharmaceuticals, we look forward to continuing to work with the Division to facilitate the review of this application. If you have any questions or need additional information during the review, please contact the undersigned, Kimberly S. Stranick, Ph.D., at (908) 304 6580 or. in my absence, Eric A. Floyd, Ph.D., at (908) 231 2474.

Sincerely,

Kimberly S. Stranick, Ph.D. Director, Regulatory Liaison

Limberly Stranick

US Regulatory Affairs

Attachment

Enclosures:

Electronic archival copy: 1 CD-ROM labeled NDA 21-704 ALLEGRA-D 24 HOUR™ Extended Release

Tablets AMENDMENT February 17, 2004

1 paper copy of Cover Letter, Form 356h and certifications in Items 14 with original signatures

cc: Ms. Christine Yu, Regulatory Project Manager (via fax)



Food and Drug Administration Center for Drug Evaluation and Research Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET					
DATE:	February 13, 2004		Car		
To:	Kimberly S. Stranick, Ph. Director, US Regulatory		From: Christine Yu, R.Ph.  Regulatory Management Officer		
Company: Aventis Pharmaceuticals, Inc.		Inc.	Division of Pulmonary & Allergy Drug Products		
Fax number: 908-304-6317		<u>-</u>	Fax number: 301-827-1271		
Phone number: 908-304-6580			Phone number: 301-827-1051		
Subject:	NDA 21-704 Allegra-D 24 Request for CMC information				
Total no.	of pages including cover:	2			
Comment	s:				
Document	to be mailed:	□ YES	√ NO		

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at 301-827-1050. Thank you.

# NDA 21-704 Information Request February 13, 2004 Page 2

We refer to your original NDA 21-704 submitted December 19, 2003. We note that you have provided cross references to approved NDAs, supplements, and annual reports for the Chemistry, Manufacturing and Controls portions of your application. In order to facilitate the review of your NDA, please provide the following information:

- 1. The name, location, contact persons, current status, and CFN numbers of all the current manufacturers/suppliers, packagers, and testers of **Fexofenadine HCl**.
- 2. The Drug Master File (DMF) numbers and Letters of Authorization (LOAs) from the above manufacturers/suppliers.
- 3. The most current approved specifications with all acceptance criteria.

If you have questions about the contents of this facsimile, please contact Ms. Christine Yu at 301-827-1051.

Appears This Way On Original



# DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration Rockville, MD 20857

NDA 21-704

Aventis Pharmaceuticals, Inc. 200 Crossing Blvd. P.O. Box 6890 Bridgewater, NJ 08807-0890

Attention:

Kimberly Stranick, Ph.D.

Director, Regulatory Liaison

Dear Dr. Stranick:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:

Allegra-D 24 hour (fexofenadine HCl 180 mg and

pseudoephedrine HCl 240 mg) Extended Release tablet

Review Priority Classification:

Standard (S)

Date of Application:

December 19, 2003

Date of Receipt:

December 19, 2003

Our Reference Number:

NDA 21-704

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 17, 2004, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 19, 2004.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are waiving the requirement for pediatric studies for this application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

NDA 21-704 Page 2

# U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary & Allergy Drug Products, HFD-570
Attention: Division Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Ms. Christine Yu, R.Ph., Regulatory Project Manager, at (301) 827-1051.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ALLEGRA-D 24 HOUR Extended Release Tablet (fexofenadine HCl 180 mg and pseudoephedrine HCl 240 mg)



December 1, 2003

Mellon Bank Three Mellon Bank Center 27<sup>th</sup> floor (FDA 360909) Pittsburgh, PA 15259-0001

RE: User Fee for M016455/ fexofenadine HCl 180mg + pseudoephedrine HCl 240mg NDA # 21-704 (N021704)

To whom it may concern:

Please find enclosed the User Fee payment in the amount of \$286,750.00 for the upcoming ALLEGRA-D 24 HOUR<sup>TM</sup> (M016455 / fexofenadine HCl 180mg + pseudoephedrine HCl 240mg) Extended-Release Tablet NDA submission. The User fee ID No. for this submission is 4645.

If you have any questions or if I can be of further assistance, please contact me.

Sincerely yours,

Cin d. Hogel for S.C. Steve Caffé. M.D.

Vice President, Head US Regulatory Affairs Tel (908) 231 5863 or (908) 304 6580 ALLEGRA-D 24 HOUR Extended Release Tablet (fexofenadine HCl 180 mg and pseudoephedrine HCl 240 mg)

DEPARTMENT OF HEALTH AND HUMAN SERVICES	PRESCRIPTION DRUG Form Approved: OMB No. 0910-029 Expiration Date: February 29, 2004.			
FOOD AND DRUG ADMINISTRATION	USER FEE COVER SHEET			
	rerse Side Before Completing This Form			
A completed form must be signed and accompany each new d reverse side. If payment is sent by U.S. mall or counter, please in can be found on CDER's website: http://www.fda.gov/cder/pdufa/c	drug or biologic product application and each new supplement. See exceptions on the include a copy of this completed form with payment. Payment instructions and fee rates /clefault.htm			
1. APPLICANT'S NAME AND ADDRESS	4. BLA SUBMISSION TRACKING NUMBER (STN) / NOA NUMBER			
Aventis Pharmaceuticals, Inc. 200 Crossing Boulevard P.O. Box 6890	N021704  5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?			
Bridgewater, NJ 08807-0890	IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE			
	AND SIGN THIS FORM.  IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:			
	THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.			
2. TELEPHONE NUMBER (Include Area Code)	THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:			
( 908 ) 304-6580	(APPLICATION NO. CONTAINING THE DATA).			
3. PRODUCT NAME	6. USER FEE I.D. NUMBER			
Fexofenadine Hydrochloride (INN) 180 mg and Pseudoephe Hydrochloride (INN) 240 mg - ALLEGRA-D 24 HOUR(TM)	10-10 (Basigned 11 November 2005)			
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USE	ER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.			
A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See Item 7, reverse side before checking box.)			
THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal F Drug, and Cosmetic Act (See item 7, reverse side before checking box.)	GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY (Self Explanatory)			
8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS	IS APPLICATION? YES Z NO			
**************************************	(See Item 8, reverse side If answered YES)			
was seed to a secretary existing data sources, datherny and main	is estimated to average 30 minutes per response, including the time for reviewing intaining the data needed, and completing and reviewing the collection of information. of this collection of information, including suggestions for reducing this burden to:			
Food and Drug Administration CDER, HFD-	displays a currently valid OMB control number.			
SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE DATE			
-baff	Steve Caffe, MD Head, US Regulatory Affairs 12/01/2003			

## Memorandum of Telephone Facsimile Correspondence

Date:

September 25, 2003

To:

Kimberly S. Stranick, Ph.D.

Director, U.S. Regulatory Affairs

Fax:

908-304-6317

From:

Christine Yu, R.Ph. Regulatory Management Officer

Subject:

IND 66,289 for fexofenad de HCl/pseudoephrine HCl 24-hour ER tablets

Minutes of August 27, 2003 pre-NDA meeting

Reference is made to the meeting/teleconference held between representatives of your company and this Division on August 27, 2003. Attached is a copy of our final minutes for that These minutes will serve as the official record of the meeting/teleconference. meeting/teleconference. If you have any questions or comments regarding the minutes, please call me at (301) 827-1051.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED. CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you received this document in error, please immediately notify us by telephone at (301) 827-1050 and return it to us at FDA, 5600 Fishers Lane, HFD-570, DPDP, Rockville, MD 20857.

Thank you.

#### **MEETING MINUTES**

DATE:

August 27, 2003

TIME:

10:30 AM - 12:00 PM

APPLICATION:

IND 66,289

TYPE:

Pre-NDA meeting

DRUG NAME:

Fexofenadine HCl/pseudoephrine HCl 24-hour ER tablets

INDICATION:

Relief of symptoms associated with SAR in adults and children 12 years

and older

IMTS#:

10791

SPONSOR:

Aventis Pharmaceuticals, Inc.

Represented by:

Eric Floyd, Regulatory Affairs

Kimberly Stranick, Regulatory Affairs Madhu Anant, Regulatory Affairs Stephen Sherman, Aventis- Canada John Gigantino, Regulatory CMC Rosemary Crew, Regulatory Operations Ian Davidson, Project Team Leader

Prafulla Agrawala, Global Project Development Rajiv Haribhakti, Global Project Development Kazimierz Chrzan, Global Project Development Doug Hatzenbuhler, Global Project Development

Barbara Kittner, Clinical

Sriram Krishnaswami, Drug Metabolism/Pharmacokinetics

Abdul Sankoh, Biostatistics

FDA attendees:

Division of Pulmonary & Allergy Drug Products, HFD-570

Brian Rogers, CMC Reviewer Edward Jao, CMC Reviewer

Guirag Poochikian, CMC Team Leader

Shinja Kim, Clinical Pharmacology & Biopharmaceutics (CPB) Reviewer

Emmanuel Fadiran, CPB Team Leader

Feng Zhou, Biometrics Reviewer

James Gebert, Biometrics Team Leader (Actg)

Charles Lee, Medical Reviewer

Lydia Gilbert-McClain, Medical Team Leader (Acting)

Carol Bosken, Medical Reviewer Badrul Chowdhury, Director

Christine Yu, Regulatory Management Officer

Eric Duffy, Director, DNDC II, HFD-820

Aventis submitted a meeting request for a pre-NDA meeting on May 30, 2003, to discuss NDA submission strategy for the "Allegra-D 24 hour" product. Briefing packages for the meeting were dated July 25, 2003. End of Phase 2 meeting for the same product was held January 29, 2002.

## Agenda (order based on the questions included in the briefing package)

Regulatory

Clinical Pharmacology & Biopharmacuetics (CPB)

Clinical

Chemistry, Manufacturing & Controls (CMC)

## Guidances for Industry referenced during the meeting

Guidances represents the Food and Drug Administration's (FDA's) current thinking on a topic. They do not create or confer any rights for or on any person and do not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

#### Minutes

The Division presented slides which included Aventis' questions, followed by the Division's responses. Discussions during the meeting are captured between the slides.

#### Regulatory

Regulatory #1.

Aventis plans to submit a new NDA instead of an Efficacy Supplement and pay a supplement fee (from discussions at the EOP2 meeting).

Based on information submitted, a supplement (1/2) fee appears to be appropriate. When the NDA is submitted, Office of Regulatory Policy (User Fees staff) will make the final determination of the fee required and contact Aventis if any adjustment needs to be made.

Food and Dring Administration
District of Primonary and Allergy Dring Products

Regulatory #2:

The NDA will be prepared in the NDA / Common Technical Document (CTD) hybrid format. The CMC sections will be presented as CTD formatted Modules, while the remainder of the submission will follow 356h NDA format... Requesting comments on TOC...

- Table of contents is correct with the following exceptions / notations:
  - ◆HUPHARM folder is indicated as standalone, it should be a sub-folder of HPBIO per IT3 Guidance of January, 1999, page 32.
  - ◆Your 8G and 8H entries indicate a "Clinical" folder for the ISE and ISS. Both the ISE and ISS should be sub-folders of CLINSTAT – a typo?



Regulatory #3:

Aventis intends to ... (sic) submit mixed (hybrid) submission consisting of an eNDA backbone and presentation for all except CMC which will be in the CTD module format...

...any specific recommendations or requests that will ease the review of this electronic submission?

The Guidances pertaining to this type of submission (IT 3 of 01/1999 and the Guidance for Industry: Submitting Marketing Applications According to ICH-CTD Format... of August 2001, if followed, will fulfill all the requirements needed for review of this submission.

Division of Pulmonary and Mergy Drug Products

#### Regulatory #4

A Data Correction Form will be provided in the front of each CRF. (sic) They will be bookmarked, but, no hyperlink(s) will be provided for corrected items... Does the Agency concur with this approach?

#### > Yes

- ◆ Hyperlinks to corrected items are *suggested* in the IT3 of 1/1999, however, these are only suggested as a *means of avoiding confusion* and are not required.
- Locating the Data Correction Forms immediately preceding the appropriate CRF will suffice in minimizing confusion.



Food and Drug Administrating
DMSOn of Polymonau and Allego Drug Superiors

Regulatory #5

(sic) Aventis plans to submit CRF's for AE's, Serious AE's and Pregnancy only, with others available upon request...

Does the Agency concur?

- Yes



Fito NDA #60266

#### Regulatory #6

(sic) Referring to IT3, Aventis does not plan to include Patient Profiles... Does the Agency concur with this plan?

For this submission, no Patient Profiles are needed.



#### Regulatory #7

Aventis does not plan to submit any separate document(s) equivalent to item 10 (Statistical) of the NDA. (sic) All data will be included with the study report (M016455S/100)

Does the Agency concur?

- This is perfectly acceptable according to the IT3 Guidance of 1/1999, providing proper entries and links are provided in the TOC Item #10 categories to this data.
- CPB, however, does have additional input concerning included data that will come later in this presentation.



## Clinical Pharmacology & Biopharmaceutics

#### REGULATORY

7. Aventis does not plan to submit any separate document equivalent to the Item 10 (Statistical) of the NDA. All statistical information for the pivotal bioequivalence study (M016455S/1001) will be included with the study report. Does the Agency concur?

Comment: Also include statistical information for M016455S/1002 in the study report.



## CLINICAL PHARMACOKINETICS AND BIOAVAILABILITY

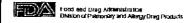
8. As discussed between the FDA and Aventis at the End of Phase II meeting, the clinical support for the approval of ALLEGRA-D 24 HOUR (fexofenadine 180 mg and pseudoephedrine 240 mg) Extended Release Tablets will be based on a pilot bioavailability study (KA467) with a prototype combination formulation, a pivotal single and multiple dose bioequivalence study (M016455S/1001) and an effect of food study (M016455S/1002) with the final combination formulation. Does the Agency concur?

Comment: We concur (CPB perspective).



9. In order to facilitate the pharmacokinetic/biostatistical review, the final concentration-time data from the pivotal BE study (M016455S/1001) will be submitted with a data description file according to electronic submission guidelines as SAS transport (.xpt) and .pdf files, respectively.

Does the Agency have any other specific requests to ease the review?



#### Comment:

- In addition to the PK parameters listed in Table 1 (page 127), obtain other PK parameters such as, T<sub>max</sub> and t<sub>1/2</sub> for fexofenadine and PSE following a single dose (i.e., after the first dose administration) and at steady state, C<sub>average</sub> and degree of fluctuation (C<sub>max</sub>-C<sub>min</sub>/C<sub>av</sub>), etc., for fexofenadine and PSE from the data M016455S/1001.
- Provide SAS transport (.xpt) and .pdf files for the data from Study M016455S/1002.



10. Aventis proposes to set dissolution specifications for pseudoephedrine HCl from the ALLEGRA-D 24 HOUR tablet as described in Section 7 of this briefing package. Does the agency concur with the proposed approach?

#### Comment:

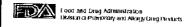
No. the IVIVC has to be externally validated before it can be used to set dissolution specification.



The Division referenced the Guidance for Industry entitled, "Extended release oral dosage forms: development, evaluation, and application of in vitro/in vivo correlations," and stated that the data from the fasted period of the food effect study may be used for the external validation of the IVIVC.

11. Fexofenadine HCl alone and in combination with pseudoephedrine HCl has been previously studied and relevant results of Phase I studies have been submitted to NDAs 20-265, 20-872 and 20-786. An overview of the results of these studies has been presented in this document in summary tables (Section 7.4, Summary Table of Completed Studies). Aventis proposes to include the same tables in the NDA and not include the full study reports. No additional Phase I studies beyond those already submitted are planned for the ALLEGRA-D 24 HOUR NDA. Does the Agency concur?

Comment: We concur.



#### Clinical comments

## Clinical Comments

- As part of your Integrated Summary of Safety, submit the following:
  - ◆ A review of the medical literature published since the approval of Allegra tablets, NDA 20-872, on February 25, 2000, focusing on the safety of fexofenadine. Also submit a review of the published medical literature focusing on the safety of pseudoephedrine HCl.
  - A summary, review, and analysis of worldwide postmarketing adverse event reports for fexofenadine and pseudoephedrine HCI.



#### Post-meeting addendum-

In response to a post-meeting request from Aventis regarding the second bullet above and discussion at the meeting, the Division provides the following clarification.

Summary, review, and analysis of postmarketing adverse event reports for the currently marketed twice daily formulation of Allegra-D (fexofenadine 60 mg/pseudoephedrine 120 mg) tablets would provide the information needed for review of the NDA.

On a separate note, Aventis stated that the adverse events data in the package insert will not be recoded from MMDWHO to MeDRA. This was acceptable to the Division.

## Chemistry, Manufacturing and Controls

Question 12. Format and content of CMC documentation

See response for Regulatory question 2.

Resolved Blog, Administration

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Question 13. Pseudoephedrine HCl Drug Substance Particle Size Effect on Dissolution

Table 5.2.1- 1 Particle Size Description for Developmental and NDA Stability Batches

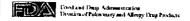
The data from all these batches will be provided in the pharmaceutical development section of the NDA. The data demonstrate that particle size has no impact on dissolution properties as measured by the dissolution similarity factor 12 calculation. (Guidance for Industry: Immediate Release Solid Oral Dosage Forms, Scale-up and Post Approval Changes: Chemistry, Biosequivalence Documentation: (CDER November 1995). The comparison analysis for these batches will be presented in the NDA.

Does the Agency agree that this approach is acceptable for defining the particle size specification for pseudoephedrine HCl?

#### Question 13

#### Response

- There is insufficient data presented to evaluate the adequacy of this approach.
- The test method used for dissolution measurement must be agreed to prior to evaluation of the associated data and must have adequate discriminating ability.
- Dissolution may be affected by a combination of independent variables that are affected by or influence the affect of particle size. In other words, other variables may have an effect on the dissolution rate as a function of particle size
- J. Thus the performance over the shelf-life within the range of formulation and manufacturing parameters used in the critical batches will also need to be taken into account when setting acceptance criteria.



In response to the second bullet above, Aventis stated that they had found the dissolution test method to be adequately discriminating, but they will make sure to get the Agency's agreement on the method before evaluating the data.

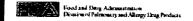
The Division noted that agreement should be reached as soon as possible, preferably before the stability studies are initiated.

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#### **Question 13**

#### Response (cont'd)

- Please explain the use of batches of pseudoephedrine HCl in one batch of drug product. The utility of this approach is unclear.
- Please note that the SUPAC modified release guidance for solid oral dosage forms must be referenced for the appropriate comparison criteria and calculations.



Regarding the first bullet in the slide above, Aventis replied that  $\Gamma$ 

J Additionally, they stated that particle size of the drug substance did not affect dissolution. Although they will submit the data, release of particles were independent of PSE particle size. L

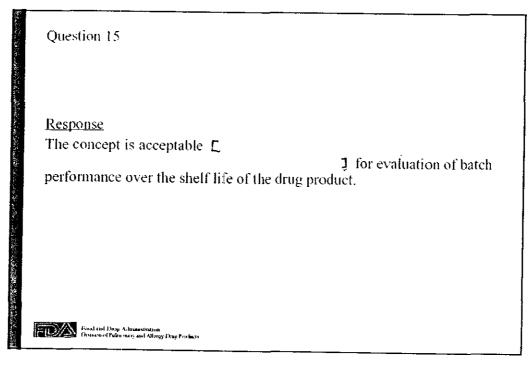
The Division noted Aventis rationale but recommended that the PSE particle size still be constrained to a reasonable range.

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		_
Question 14. In-Process Tests for Commercial Product		
Ľ.		
Does the Agency agree with this proposal?	J	
Ford and Drug Administration Decision of Pulsamenty and Affence Drug Francis  Question 14		
Response The proposed in-process testing may be adequate if batch-to-batch and beginning- to end-of-batch variability are shown to be adequately controlled.		

Food and they definite restroy
Done on of Point cary and Allerry Drug Products

Question 15. Pseudoephedrine HCl Dissolution Pro	ofile
Aventis proposes using [	
	٦
Does the Agency agree with this proposal?	-å
Food and Drug Adams stration Desirion of Falmona spand Allergy Drug Products	



Drug	_
Aventi	proposes to C
Does t	e Agency agree with this proposal?
Does to	
Respor Yes, th	

Question 17. C J Dissolution Test Method

To address FDA comments from EOP II meeting regarding the L J dissolution testing. Aventis proposes to provide dissolution data for pseudoephedrine HCl measured using the proposed test method L

J

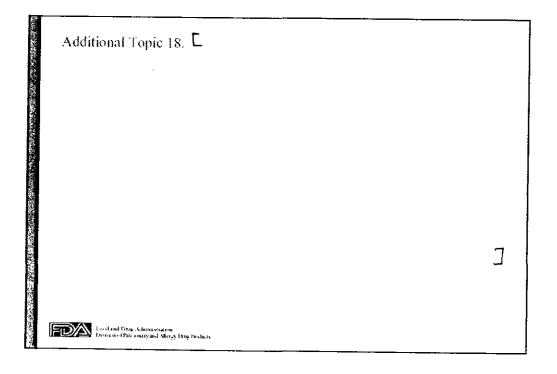
Does the Agency accept this as addressing their request that pseudoephedrine dissolution data be generated  $\boldsymbol{\zeta}$ 

J



Dagnanus	
Response  Dissolution data C	7
	J must be
evaluated by both the CMC and Bioph	
on a dissolution method and associated	- · · · · · · · · · · · · · · · · · · ·
have not provided data for evaluation,	•
appropriateness of the proposed parame	eters for the dissolution test
method.	
Provide dissolution data as requested in	the EOD? meeting
1 To vide dissolution data as requested in	rue LOF2 meeting.

Aventis responded that stability studies have been ongoing for —months. Data will be provided in the NDA.

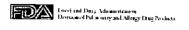


Additional To	pic 18			
Response . L				
		J		-
Fuestand Day, Addition of Labora	namstektum 17 and Allengy Daug Pechecis			

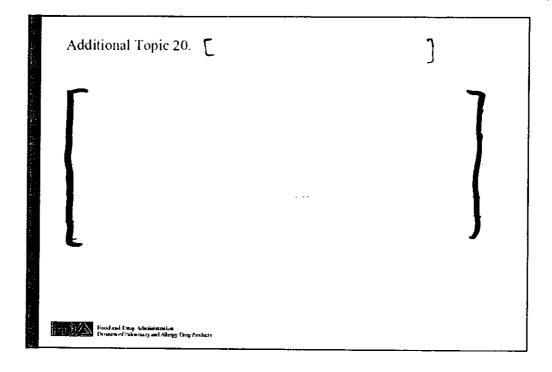
Additional Topic 19. Fexofenadine HCl Drug Substance Particle Size.

Aventis has a batch history of L

J No changes to existing specifications are proposed, and, Aventis believes that additional evaluations of fexofenadine HCl dissolution performance (C) I are unnecessary.



	Additional Topic 19
The second secon	Response  This is acceptable for the \( \textstyle \) provided that all manufacturing parameters are well defined and the stability data confirm reproducible stability results.
an artist of	Food and Drug Administration Division of Polisionary and Allergy Drug Products



Response
Please comment on why

Additional Topic 21. Stability Database/Commitment.

As discussed during the End of Phase II meeting, Aventis will submit 12-months of ICH stability data for three batches in the NDA, and propose a 24-month expiration based upon the submitted database and the known stability of these drug substances. Statistical analyses will be performed on the assay and impurities data. Aventis will place the first three commercial production batches of this product on controlled room temperature (25°C/60% RH) stability and one batch annually thereafter. Aventis has made the recommended changes to the matrix stability protocol.

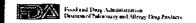


#### Additional Topic 21

#### Response

Determination of the expiration dating period will be based upon statistical evaluation of all relevant parameters and must be calculated from real-time data. Differences in the stability data between similar containers may preclude poolability and hence adversely affect the calculated expiration dating period.

You must demonstrate that all physicochemical characteristics and functionality of the two proposed blister units are equivalent. If they show different characteristics or functionality and demonstrate different behavior on stability testing, then the container system that provides the least protection will be the limiting factor and be used to determine the expiration dating period.



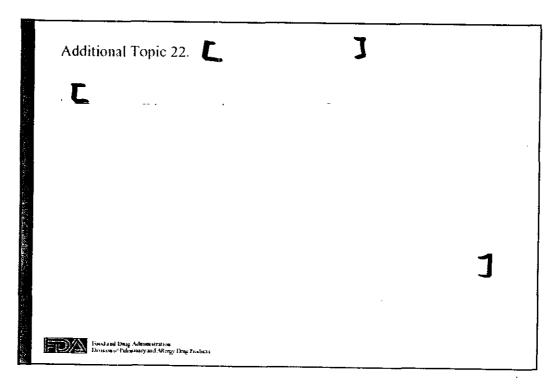
#### Additional Topic 21

#### Response (Cont'd)

Considering the post-approval problems associated with Allegra-D 12 HOUR, and in order to confirm the proposed expiration dating period, the number of batches placed annually in the stability testing program must be L J of the production rate. Submit a proposal in the NDA L J This rate of batch stability testing will need to be implemented until the drug product stability and performance characteristics are verified.

The first three post-approval production-scale batches must be placed under accelerated storage conditions (40°C/75°% RH) if the NDA stability batches are not production-scale batches.





Upon inquiry from the Division, Aventis responded that E

j is not an option.

Additional Topic 23. Fexofenadine HCl content uniformity.

Aventis has performed process development studies to assure the fexofenadine HCl content consistently meets the USP acceptance criteria. These studies include full-scale manufacturing batches, and will be reported in the NDA.

#### Response

The acceptance criteria must be reflective of the current manufacturing capability.

Abnormal variability of the fexofenadine HCI content may indicate manufacturing problems that must be resolved. Therefore the acceptance criteria for content uniformity must be established to the manufacturing capability.



Additional Topic 24.		3	
			]
Response Satisfactory. [	]		
fried and Dang Administration Decreased Philipmary and Allergy Drug Perchases			

Additional Topic 25. Label claim of pseudoephedrine HCl.

Response Satisfactory



Additional Topic 26. Label claim of fexofenadine HCl.

Fexofenadine HC1 C development batch manufacture, C

During early

work identified the

Response Satisfactory



Additional Topic 27. DMF Letters of Access.

DMF Letters of Access for all noncompendial excipients will be provided in the NDA.

Response Satisfactory



Experient Desp Administration Presistant Pulms story and Allergy Drug Feedbase

Additional Topic 28. Release and Stability Tests for Comn	nercial Product.
Aventis will employ L  NDA stability batches. (See meeting package)	1
Response	
Food and Drug Administration Distributed of Polymonary and Allergy Drug Products	

Aventis stated [

The Division recommended establishment of the — test method. Regarding a proposal to destablishment of the — test method. Regarding a proposal to destablishment of the — test method. Regarding a proposal to destablishment of the — test method. Regarding a proposal to destablishment of the — test method. Regarding a proposal to destablishment of the — test method. Regarding a proposal test destablishment of the — test method. Regarding a proposal test destablishment of the — test method. Regarding a proposal test destablishment of the — test method. Regarding a proposal test destablishment of the — test method. Regarding a proposal test destablishment of the — test method. Regarding a proposal test destablishment of the — test method. Regarding a proposal test destablishment of the — test method. Regarding a proposal test destablishment of the — test method. Regarding a proposal test destablishment of the — test method. Regarding a proposal test destablishment of the — test method. Regarding a proposal test destablishment of the — test method. Regarding a proposal test destablishment of the — test method. Regarding a proposal test destablishment of the proposal tes

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Additional Comment to Sponsor

Provide representative Certificates of Analysis for all formulation components, including both drug substances.

The meeting was adjourned at this time.

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/s/

Christine Yu 9/25/03 06:05:43 PM

## Memorandum of Telephone Facsimile Correspondence

Date:

July 18, 2002

To:

Eric Floyd, Ph.D.

Senior Director, Drug Regulatory Affairs

Fax:

908-231-3734

From:

Christine Yu, R.Ph.

Regulatory Project Manager

Subject:

IND 48,486 Allegra-D 24-hour extended-release tablets

EOP2 January 29, 2002, Meeting Minutes

Reference is made to the meeting held between representatives of your company and this Division on January 29, 2002. Attached is a copy of our final minutes for that meeting/teleconference. These minutes will serve as the official record of the meeting/teleconference. If you have any questions or comments regarding the minutes, please call me at (301) 827-1051.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you received this document in error, please immediately notify us by telephone at (301) 827-1050 and return it to us at FDA, 5600 Fishers Lane, HFD-570, DPDP, Rockville, MD 20857.

Thank you.

#### INDUSTRY MEETING MINUTES

DATE:

January 29, 2002

LOCATION:

Parklawn Chesapeake Conference Room

Time:

1:30-3:00pm IND 48,486

APPLICATION: DRUG NAME:

Allegra-D (fexofenadine HCl 180 mg/pseudoephedrine HCl 240 mg)

24-hour extended-release tablets

SPONSOR:

Aventis Pharmaceuticals

BETWEEN:

Barbara Kittner, Clinical Manager

Susan Witham, Drug Regulatory Affairs Eric Floyd, Drug Regulatory Affairs

C

J CMC)

Damayanthi Devineni, Biopharmaceuticals Sriram Krishnaswami, Biopharmaceuticals Rajiv Haribhakti, Pharmaceutical Development Kaz Chrzan, Pharmaceutical Development Prafulla Agrawal, Pharmaceutical Development

AND

Division of Pulmonary & Allergy Drug Products, unless noted otherwise

Badrul Chowdhury, Medical Team Leader

Eric Duff Director, Division of New Drug Chemistry II

Emmanuel Fadiran, Clinical Pharmacology & Biopharmaceutics TL

James Gebert, Biostatistics Team Leader

Shinja Kim, Clinical Pharmacology & Biopharmaceutics Reviewer

Charles Lee, Medical Reviewer Marianne Mann, Acting Director Mary Purucker, Medical Team Leader Brian Rogers, Chemistry Reviewer Jehan Rowlands, Post-doctoral fellow

Sandra Suarez, Clinical Pharmacology & Biopharmaceutics Reviewer

Christine Yu, Regulatory Project Manager Feng Zhou, Mathematical Statistician

#### **Background**

Aventis Pharmaceutials requested an End-of-Phase II meeting to discuss with the Division their proposal for a 180 mg fexofendine and 240 mg pseudoephedrine extended-release tablet for once-a-day administration in treatment of seasonal allergic rhinitis in patients 12-years and older. The briefing package was received November 15, 2001.

## Order of Agenda (based on questions submitted in briefing package)

Aventis presentation (3 slides)

- A. Regulatory & related question #3 under Clinical Pharmacology
- B. Chemistry, Manufacturing, and Control (CMC)
- C. Clinical Pharmacology
- D. Clinical
- E. Labeling Question

#### **Minutes Format**

Aventis' questions from the briefing package are noted in Italics font, followed by the Division's responses and discussion in normal font.

Appendix A contains slides presented by Aventis during the meeting.

Appendix B contains slides presented by the Division during the meeting.

Appendix C contains CMC information presented during the meeting and faxed to Aventis on February 25, 2002.

## Guidances for Industry referenced during the meeting

Note that guidances are not binding but rather represent the Agency's current thinking on the issue. Alternative approaches may be acceptable. Some guidances are in draft form for public comment. The content of draft guidances can change based on the review of public comments or other events.

#### **Minutes**

Aventis presented 3 slides highlighting details about the proposed drug product and the manufacturing process. The proposed drug product [

## A. Regulatory & Question #3 under Clinical Pharmacology

## 1. Question #3 under Clinical Pharmacology

Aventis plans to conduct these bioequivalence and food effect studies under the Allegra-D IND 48,486. Does the Division agree with this approach?

The Division does not agree. The new Allegra-D 24-hour formulation has an entirely different extended-release mechanism from the Allegra-D 12-hour formulation. The Division stated that since the two formulations are entirely different, a new IND should be submitted for the Allegra-D 24-hour formulation.

Aventis asked if the new IND may be waived of the 30-day safety waiting period.

The Division responded that with the submission of the new IND for the 24-hour formulation, Aventis can request a waiver of the 30-day safety waiting period.

## 2. Regulatory

Aventis plans to submit the new formulation and dosage regimen as an efficacy supplement under the Allegra-D NDA 20-786. Does the Division agree with this approach?

The Division does not agree. For the same reasons stated in Question 3 under Clinical Pharmacology, a new NDA should be submitted for the Allegra-D 24-hour formulation.

### B. Chemistry, Manufacturing & Controls

1. Aventis will be providing, in the efficacy supplement for the new formulation, stability data from three pilot scale-up batches. Aventis would like to submit the \(\subseteq\) 1 data from the three pilot scale-up batches with the initial filing of the supplement, then submit the \(\subseteq\) 3 and 12-month data at the 4-month safety update and prior to taking action on the NDA Supplement, respectively. Does the Division agree with this approach?

Submit 12 months stability data with the application. Additional data may be submitted during the review process to support the proposed expiry.

2. Allegra-D — stability data is expected to have a similar stability profile as observed for other formulations of fexofenadine HCl or pseudoephedrine HCl. Therefore, Aventis is proposing a 24-month expiry period with a commitment to place the first three marketed batches on stability. Does the Division agree with this approach?

A 24-month expiry may be proposed. The labeled expiry will be based on the quality and extent of stability data received.

- 3. Please confirm that our proposed product specifications are acceptable, recognizing that dissolution specifications will be redefined based on NDA registration batch data.
  - Product specifications will be based upon the data from all critical batches, including
    the available stability data. Since neither appropriate methods nor data for dissolution
    are provided, comments are withheld at this time.
  - The specification should contain a second identity test that is not based on

    I (HPLC acceptable, 'not acceptable).
  - We expect that the related impurities specifications will be as tight or tighter than those for Allegra-D 12-Hour Tablets. Also, the acceptance criteria for process-related impurities must be listed and included in the limits for Total Related Impurities. A footnote may be added to clarify that the process-related impurities are analyzed at the drug substance level. A parameter for Individual Unspecified Impurities must be

included with limits of Less Than [ ] Also, the parameter Total Unspecified Impurities must be included and limits set.

•	ine limits for related impurities must be provided for two significant figures. L d
=	The levels L I should be minimized.
•	Among other variables, C
	I should be evaluated. The registration stability batches must be manufactured and placed on stability only after you establish the optimized parameters for this drug product.
•	A specification for Karl Fisher moisture content must be included. Acceptance criterion must be based upon the levels validated in the previously mentioned study.
•	Owing to the possibly inaccurate nature of the fexofenadine HCl appropriate validation studies must be accomplished to demonstrate the suitability of the for the fexofenadine HCl D These validation studies must include scale-up and process variable effects.
•	We expect 100% inspection for C
•	We note that the assay values for pseudoephedrine HCl are \( \tau \) in the data for the assay values for fexofenadine HCl are \( \tau \) in the data for the developmental batches on page 32, 40, 58, 60, 72, 74, etc. Manufacture of the pseudoephedrine \( \tau \) it the fexofenadine \( \tau \)
•	Letter of authorization (LOA) for Drug Master Files (DMFs) will be needed for all non-compendial excipients.
on cui	entis has proposed a matrix program for the Allegra-D—' batches which will be placed stability for the new formulation. The proposed stability matrix program is based on the rrently known stability information for the new Allegra-D— formulation development tches and stability data of marketed Allegra products. The enclosed matrix stability

protocol is based on the draft stability guidance document and we believe it meets the

the stability protocol, including the testing to be performed, is acceptable.

matrixing design package product evaluations. Please confirm that

4.

criteria for

The protocol needs to be modified to provide for testing of all presentations at 12 and 24 months since 12 months data is required at submission and a 24-month expiry is being proposed.

5. Note that the dissolution method we have been using for this new formulation has C

Aventis proposes to collect data using

7 Does the Division have

any comments on this plan?

- Product specifications will be based upon the data from all critical batches, including
  the available stability data. Since neither appropriate methods nor data for dissolution
  are provided, comments are withheld.
- [

J

- We also refer to the previous comment 3 C
- Recommendations for media and dissolution conditions will be addressed by the Clinical Pharmacology & Biopharmaceutics reviewer.
- C. Clinical Pharmacology & Biopharmaceutics
  - 1. Response to question #5 under CMC

In selecting the dissolution method, consider the effect of medium (pH), apparatus and speed on the dissolution of both components of the formulation. Also provide the optimized dissolution method with specifications for fexofenadine and pseudoephedrine.

2. Aventis will be conducting a bioequivalence study and a food effect study to support the approval of the new formulation for Allegra-D (180 mg fexofenadine HCl and 240 mg pseudoephedrine HCl) extended-release tablets taken once a day. Does the Division agree with this approach?

Conduct a multiple dose study (to characterize the steady state performance of the product).

- 3. Does the Division have any comments on the study designs proposed for the bioequivalence and food effect studies?
  - a. Please include females in the proposed studies. Consider the following statements in the FDA guidances:
    - "If the drug product is intended for use in both sexes, the sponsor should attempt to includes similar proportions of males and females in the study" (Guidance for Industry, "Bioavailability and Bioequivalence studies for orally administered drug products- General considerations").
    - "Gender should not be an inclusion criteria" (Guidance for Industry, "Study and evaluation of gender differences in the clinical evaluation of drugs").
  - b. Please set the confidence interval for food effect on C max to 80 to 125% or provide justification (PK/PD relationship) for using a different criterion.
  - c. The to-be marketed formulation should be used for these studies. If not, then Aventis should link the formulation used in these studies (i.e., BE/food effect) to the to-be marketed formulation.

#### D. Clinical

#### 1. Protocol comments

- It is not acceptable to exclude females from the pivotal bioequivalence and food effect studies. Gender should not be an inclusion criterion. Females should be represented in the BE studies, and not uniformly excluded as per the current protocols.
- We strongly recommend that you use the final, to-be-marketed formulation in the pivotal studies
- Provide data for C min in addition to AUC and C max. We will look at data for C min to support end-of-dosing-interval bioavailability.
- Safety endpoints are acceptable.

#### 2. Additional comments

There is evidence that grapefruit and apple juices affect fexofenadine bioavailability. It is recommended that you study the effects of apple and grapefruit juices on fexofenadine bioavailability.

- It appears that the proposed trade name for your product is "Allegra ' The trade name is not likely to be acceptable. An alternative trade name would be "Allegra-D 24 Hour," which more accurately reflects the proposed dosing interval.
- Upon approval, the trade name of the current Allegra-D (12-hour dosing) product must be changed accordingly to decrease confusion with the new product. An alternative trade name for the current product would be "Allegra-D 12 Hour."

## 3. Clinical question from briefing package

Aventis will be requesting an official waiver of pediatric studies as currently required by the Pediatric Rule based on the amount of pseudoephedrine contained in the new formulation, and that it is unsafe for children under the age of 12 years. Does the Division agree that pediatric studies in children under the age of 12 years will not be required in order to get approval for the new Allegra-D formulation?

Pediatric studies will not be required for approval of the Allegra-D 24-hour formulation.

#### E. Labeling Question

Three studies evaluating special populations in renally-impaired, hepatically-impaired patients and elderly patients were previously submitted and reviewed under NDAs 20-872 and 20-786. These studies support the current approved labeling for Allegra-D and Allegra tablets. Aventis is planning to submit draft labeling for the new Allegra-D formulation which will provide the same text that is currently in the Allegra labeling under Special Populations. Does the Division agree with this proposal?

- The Special Populations section of the current Allegra-D label will not be acceptable for the new formulation. The current labeling contains a recommended starting dose for renally-impaired patients. This is likely to be an inappropriate starting dose of the new Allegra-D formulation for renally-impaired patients.
- You must be prepared to support your recommendations, including recommended dose, if you propose use of this product in this population.

The meeting concluded at this time.

# 13 Page(s) Withheld

- § 552(b)(4) Trade Secret / Confidential
- § 552(b)(5) Deliberative Process
- \_\_\_\_\_ § 552(b)(5) Draft Labeling

#### Yu, Christine

om:

Jones, Michael D

∌nt:

Friday, January 25, 2002 4:21 PM

⁻ío: Cc: Mann, Marianne C

Subject:

Yu, Christine; Jones, Michael D; Brice, Tawni M; Friedman, Beverly J RE: follow-up on our dosage form question: Allegra D-24 hour tablets

#### Marianne

It sure seemed like the two drug products were quite different. However, they appeared to both be extended release tablets (with the same ACTIVE ingredients). The only way that I thought that you could "make" them come in as a separate NDA was the excepient clause. I gather from what you tell me that won't do the trick either.

That just leaves us the administrative convenience route. If they want to submit a supplement they could. But we could ask for an NDA for our own administrative convenience but would assess the new NDA as if it were a supplement.

It looks like from what you tell me the "precedent" case was administered correctly, however, it does not seem to directly correspond to our current problem so I don't see any "precedent" problems.

So ... if the new novel extended release tablet is not a new dosage form (Orange Book terms) nor is it a new route of administration (Orange Book terms) nor can we use the excepient argument, it looks like a supplement fee. It should be documented (a memo to the file would be appropriate) when the application comes in why we are charge a 1/2 fee rather than a full NDA fee.

If you wish you can speak to the applicant and tell them our determination giving the caveat that if things change once we receive the application (e.g., it really wasn't a tablet, but a capsule) our determination may change.

I hope this is helpful.

it me know how it goes.

#### ı∕like

-----Original Message-----

From:

Mann, Marianne C

Sent:

Friday, January 25, 2002 3:58 PM

To:

Jones, Michael D

Cc:

Yu, Christine

Subject:

follow-up on our dosage form question: Allegra D-24 hour tablets

#### Hi Mike

Chris Yu already posed the question to you about whether Aventis pharmaceuticals could submit their data for Allegra-D-24 hour tablets under their current NDA for Allegra-D-12 hour tablets.

You had replied that there is a clause, under exipients, in the bundling policy that states:

"Differences in excipients that require separate clinical studies of safety or effectiveness should not be included in the same original application."

In this situation, the new Allegra-D-24 hour formulation is QUITE different, but there are no exipients that require additional separate clinical studies. Nonetheless, our chemists assure me that the Allegra-D-24 hour drug product is entirely novel, and quite different from, the Allegra-D-12 hour drug product. Their application will consist of appropriate chemistry information, a single crossover bioequivalence study, and a single-crossover food effect study. It's fairly straight-forward in this regard.

At our meeting with the sponsor, I was going to therefore tell them that we would ask for a separate NDA for the Allegra-D-24 hour drug product. As for user fees, I would leave it to your consideration as to whether or not they should pay a FULL fee, or a supplemental fee.

The only clear precedence we have for this is Claritin-D-12 and Claritin-D-24 hour tablets----which were approved under separate NDAs. I believe they each paid full user fees, and that the sponsor did not "bundle" because the initial

submission was not approved......and therefore they couldn't "bundle."

Please let me know if you agree with my position! Thanks for your input on this! If you have any input on the user fee, I could share this with them, but if you'd prefer to wait till the application arrives.......! will not commit!~

-Marianne (deputy in DPADP)

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